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Volume 7 Number 1

INSULIN

RUSSELL M. WILDER

THE production of a pancreatic extract containing the antidiabetic hormone, suitable for the treatment of patients with diabetes, is one of the greatest medical achievements of the time, and marks the culmination of a series of investigations instituted by the important discovery of von Mering and Minkowski in 1889. It is interesting that years before the time of Minkowski, numerous clinicians had commented on the occasional association of diabetes and pancreatic disease, and yet no one had successfully determined the activities of the pancreas in sugar metabolism. Science advances thus haltingly. The distinguished anatomist, Conrad Brunner, in 1682 to 1683, was the first to attempt the extirpation of the pancreas in animals. The great Claude Bernard was engaged in this problem and attempted ablation of the pancreas by various means without obtaining any clue to its rôle in diabetes. Von Mering and Minkowski, in their original paper, refer to the experiments of the celebrated American surgeon, Nicholas Senn, who, in 1886, attempted total extirpation of the pancreas. The dogs and cats who were thus operated on died in from two hours to nine days, partly from the effects of the operation, partly from gangrene of the bowel, and peritonitis. One dog who lived nine days retained a good appetite and consumed ample food to the last, and yet lost five pounds in weight. Probably this dog had diabetes, but, unfortunately, there is no record that the urine was examined for sugar. It was the work of von Mering and Minkowski which

proved that the pancreas functions in sugar metabolism. The complete removal of this organ from dogs, cats, swine, and frogs resulted in severe diabetes, while partial removal, as was shown a little later by Minkowski, resulted in a more chronic and milder form of the disease.

THE PANCREAS AS A GLAND OF INTERNAL SECRETION

Lepine first advanced the theory that the pancreas functions as a gland of internal secretion. Later, this view was strengthened by the studies of anatomists, and a better appreciation of the significance of the islands of Langerhans, and of the intimate relation of these to the blood-vessels around them. The island cells have a common origin with the acinous tissue from the duct epithelium, but early become separated and differentiated from the acinous cells, and thereafter retain their individuality. They are richly supplied with blood by special capillary nets that have been compared aptly to the glomeruli of the kidneys. Furthermore, collateral advances made in the study of other glands of internal secretion, especially the thyroid and the adrenal, and the successful preparation of extracts of these, supported the theory, and kept alive the hope that it would be possible to prepare an equally active extract of the pancreas. However, failure long attended direct attack on the problem. Numerous trials of pancreatic feedings were attempted without success. The results from grafted pancreatic tissue were encouraging insomuch as they showed that animals would live long after pancreatectomy if bits of pancreas were grafted under the skin, but such procedures offered nothing as a method of treating diabetes in man, because grafts that were made from one animal species into another invariably atrophied. This subject was investigated very thoroughly by Minkowski. Further good evidence of the existence of a pancreatic internal secretion was obtained by the work of Clarke, a brilliant young scientist whose promising career was arrested by the influenza epidemic of 1918. Clarke removed the heart and pancreas of animals and perfused these organs with Locke's solution, containing glucose, finding that sugar disappeared into the heart more rapidly when the

circuit included the pancreas, than when the heart alone was perfused. Something was added to the Locke solution, or the sugar was changed in its passage through the pancreas. In the course of this study, Clarke made another discovery which is probably of fundamental importance, that the sugar suffers an alteration of its specific rotation on passing through the pancreas. Normally, glucose rotates the plane of polarized light well to the right; its specific rotation is plus 52 degrees, but the solutions that had been through the pancreas, although they contained the same amount of sugar, as was proved by their ability to reduce alkaline copper solutions, no longer rotated normally. Here was evidence, therefore, that the pancreas acted directly upon glucose.

DERIVATION OF PANCREATIC EXTRACTS AND INSULIN

Numerous attempts have been made to prepare extracts of the pancreas. Those of Murlin and Kramer, Kleiner, and Scott should be mentioned in particular, because there is good reason to believe that each of these investigators obtained active extracts; yet it must be added that none of them were sufficiently encouraged by their initial results to undertake the preparation of extracts suitable for use on patients.

It is to the Canadian investigators, Banting and Best, and their collaborators in the University of Toronto that the credit must be given for the development of insulin. The pioneering was conceived and executed by Banting and Best in the physiologic laboratories of Professor Macleod. The first patient received an extract made from the pancreas of fetal calves, on January 10, 1922. Later, developments permitted the preparation of active extracts from adult animals from the slaughter house. Recognizing the importance of the early results, Professors Macleod, Collip, Graham, Doctors Campbell and Fletcher and others in the Departments of Physiology and Medicine, University of Toronto, became engaged in the investigation, and as a result of the splendid coöperation of this able group of investigators and clinicians, progress was rapid. Protein-free extracts were prepared in quantity, a large group of

patients was treated, and the therapeutic value of insulin was definitely established. There remained, then, the problem of how best to introduce insulin to the medical world.

INTRODUCTION OF INSULIN TO MEDICAL WORLD

Certain difficulties and dangers attending the use of insulin became apparent early in the work. Preparations that had been insufficiently freed from protein caused dangerous serum reactions; overdosage with insulin, or improper buffering of the dose with food caused an abrupt depression of the blood sugar to critically low levels; occasionally, patients were made unconscious by hypoglycemia, and catastrophe was only avoided by the constant watchfulness of the clinicians and prompt restorative measures. One of the great obstacles to progress in its use was the inconstant potency of the various extracts; some were strong and others weak, and methods of standardization were uncertain. It was apparent that before a general distribution of insulin could be made, the most careful supervision of the manufacturing of the products would be necessary, and the profession must be carefully advised with regard to the dangers connected with its use. Accordingly, patents were applied for. These have been generously turned over to the University, and serve only to prevent exploitation. Also, the coöperation of a large and reliable pharmaceutic firm in the United States was secured, exclusive rights of manufacture being granted to this firm on condition that they permit the continued control of the product by a committee in the University of Toronto, which was organized for the purpose of insuring a satisfactory supervision. It is largely owing to the able and whole-hearted coöperation of Dr. Clowes, the director of the Lilly Research Laboratories, that methods of large-scale production have been developed so promptly, and that a supply of insulin of standard strength in an amount adequate to meet any demand is now assured.

Meanwhile, weekly allotments of insulin have been generously made to a gradually enlarging group of university hospitals, and to physicians with special facilities for treating diabetic patients.

The accumulated experience of these physicians has helped to establish the new treatment on a safe and reliable basis. Also, as a result of this policy of introducing insulin gradually, accidents have been avoided, to a great extent, and there is now a fairly large group of clinicians who have had experience, and who are prepared to assist in advising the profession in the technic of treatment.

STANDARDIZATION OF INSULIN AND DOSAGE

The preparation of insulin that is being used in the Mayo Clinic is "insulin" (Lilly), or "iletin." It is a colorless, clear, aqueous solution of the purified extract of the pancreas of adult animals from the slaughter house, and is distributed in sterile ampules of 5 c.c. capacity, each cubic centimeter containing 10 or 20 units, as indicated by the label. We have found that the 20-unit strength is the most convenient for general use. The unit is the standard established by biologic assay on healthy young rabbits. One unit of insulin, the standard proposed in Toronto, is one-third the amount of material necessary to cause convulsions by hypoglycemia in a rabbit weighing 2000 gm., previously fasted for twenty-four hours. A large number of rabbits are used for these tests, and, while individual rabbits vary considerably, the average result of an assay, conducted with large groups of rabbits is proving as satisfactory as that of other biologic products. The unit of insulin, when injected subcutaneously into the diabetic patient, will account for between 1.5 and 2 gm. of sugar. This has been checked by repeated assays made on patients in the Mayo Clinic, and if suitable patients are selected for this purpose, remarkably consistent agreement is noted between the rabbit assay and the clinical potency.

The daily dose found necessary in severe cases is from 20 to 40 units. This amount of insulin raises the patient's tolerance enough so that the diet may be increased to 2500 or 3000 calories. Occasionally, patients will require larger doses, particularly if they are febrile, or have acidosis or infectious complications, and also, rarely, in the absence of infections, for reasons thus

far unknown. We have seldom, however, found it necessary to use more than 60 units in one day in any case.

There are several good reasons for urging economy in the use of insulin. In the first place, the cost of the product is still a serious consideration, four cents a unit, or one dollar and twenty cents a day, if 30 units are used. Although the manufacturers assure us that the cost will be reduced in the near future, the methods of preparation and standardization are necessarily expensive, and it is probable that insulin will always be a considerable strain on the pockets of patients of moderate means. But more important than the question of cost, is the danger of hypoglycemia when very large doses are given. We have seldom felt justified in injecting more than 30 units at one time, or of repeating a dose as large as this in the same day; there seems to be no necessity for larger doses. The most extreme grades of acidosis, and acidosis complicated by infection, have been repeatedly controlled by 60 units, and in most of the serious cases adequate diets have been permitted with doses not exceeding 30 units each day.

INDICATIONS FOR, AND RESULTS FROM, TREATMENT WITH INSULIN

Our experience is now based on the treatment of 150 patients. At present, in the diabetic service in the Clinic, there are fifty or more patients, more than forty of whom are receiving insulin. In this group of 150, three died in the hospital. One of these (Case A407594), a very frail and emaciated, elderly man who suffered from a chronic, infectious arthritis, died from pneumonia. This patient had received insulin for two months, had gained in weight from 61.5 to 68.5 pounds, and had gained in strength sufficiently to establish himself in business in Rochester. The second death (Case A322666) might possibly have been avoided if the patient had been seen more promptly. The patient, a woman with not very severe diabetes, but with severe acidosis, entered the hospital in a critical condition and died thirty minutes after receiving 20 units of a lot of insulin that had been thoroughly tested on other patients. She

became drowsy, but not comatose, consciousness being retained until the very end. Death was precipitated by an acute dilatation of the heart. No laboratory data are available in the case, other than a blood plasma sugar determination of 400 mg. for each 100 c.c., and a determination of the carbon dioxid combining power of the blood of 18 volumes per cent. The third patient who died was a woman (Case A421838) with moderate diabetes complicated by renal insufficiency, resulting from extensive pyonephrosis. The patient developed an exacerbation of this infection shortly after her admission to the hospital, and this resulted in death seven days later. Insulin was used and controlled acidosis and glycosuria, death being caused by sepsis and uremia. On the other hand, we have had more than twenty cases of diabetic acidosis with a blood carbon dioxid combining-power of 25 or below, promptly controlled, and four patients in actual coma, restored. One of the latter (Case A409769) is now working as a "diener" in our laboratories; he has gained 30 pounds in weight since admission and appears to be perfectly healthy. His present diet of 2500 calories, permitted by 30 units of insulin each day is sufficient, and enables him to do a full day's work. The favorable effect of insulin on the azoturia of severe diabetes has been emphasized.[52]

More important, however, than the dramatic results observed in cases of acidosis, are the improvements that are noted when insulin has been used as an adjunct in the treatment of the progressive cases of diabetes of several years' standing. A considerable proportion of our cases is made up of patients who had been previously trained in the dietary management of their disease, and who had faithfully adhered to restricted diets for two or more years. Despite the diet, the majority of these patients had lost tolerance until, at the time of their readmission, they were unable to keep themselves free from sugar, or safe from impending acidosis on diets that were sufficient to meet the energy demands of their bodies at rest. Such patients have gained from 20 to 30 pounds in weight, with proportionate improvement in strength and vitality, so that nearly all of them could pass for perfectly healthy persons within a few months of

the institution of treatment with insulin. There is immense satisfaction to be derived from such results, but possibly a word of caution should be uttered against attributing to the insulin all the improvement that has occurred. A spirit of optimism and buoyant enthusiasm permeates the wards and infects us all. This, in itself, as will be recognized, is the best of medicine for the diabetic patient, and may be partly responsible for the rapid recoveries observed. The enthusiasm, however, seems to be justified, and carefully controlled observations made in the metabolism ward and, in part, reported elsewhere,[52] confirm the impression received from the general service.

A source of satisfaction is the record of cases complicated by severe infection, such as pneumonia, erysipelas, carbuncle, furunculosis, or septic gangrene. Two young children with severe diabetes have successfully passed through pneumonia. In one of these (Case A416633), a girl aged eight years, the entire left lung was involved and a fourteen-day course of pneumonia was followed by empyema, necessitating tubal drainage. For weeks the child's temperature was elevated, and her life hung in the balance. A fatal outcome from acidosis would unquestionably have occurred, had it not been prevented by the continued use of fairly large doses of insulin. A patient with erysipelas was treated successfully; several patients with the most extensive furunculosis were handled satisfactorily; three patients with rapidly spreading, septic gangrene underwent amputations and convalesced from their operations uneventfully. In these cases, control of acidosis previous to operation was impossible and, in my opinion, death could not have been avoided without insulin. A patient with a pancreatic cyst underwent operation, developing most severe glycosuria and acidosis subsequent to the operation. Even with the help of insulin it was difficult to control this. As much as 60 units a day were required, and if insulin had been withdrawn at any time, the outcome would certainly have been fatal. The results obtained in other clinics and especially those reported from Toronto, Boston, Chicago, and New York, are as encouraging as those which I have briefly reviewed.

These encouraging statements of what may be expected from

insulin must not lead to the erroneous conclusion that insulin is necessary in every case of diabetes, or that it is a specific for diabetes, or that it may be given in the haphazard way that many drugs are administered. Insulin is by no means a necessary adjunct to the treatment of the types of diabetes that are met with in the obese or the arteriosclerotic. The advantage of its use in mild, chronic cases is still an open question. In no case is it a cure in the strict sense of the word. Some patients do, indeed, show improvement in tolerance, following a period of insulin treatment, and when insulin is withdrawn, a higher tolerance may be noted than was present before; but similar results may be obtained by judicious dieting alone, and severe acidosis may also be managed successfully by measures that have been in use for many years. In this connection, it may not be amiss to mention one of our patients (Case A364193), who was brought into the hospital two years ago in complete coma. This patient was resuscitated with the usual measures, including the use of sodium bicarbonate, was dismissed from the hospital in fair condition, and has since been farming forty acres of land in Northern Minnesota. He returned recently for examination and appeared to be in excellent condition. What insulin does is to insure a definite increase of tolerance while it is being used. As a result of this increased power to burn sugar, some cases of acidosis which otherwise could not be controlled, become manageable. As a further result of the improved tolerance, the diet may be increased without straining the sugar mechanism, and by means of this higher diet the tissues of the body may be nourished back to normal. The effect of insulin in controlling the azotemia of severe diabetes has been emphasized.[52]

THE IMPORTANCE OF THE DIET IN TREATMENT WITH INSULIN

The successful management of diabetes with insulin demands even more attention to the diet than has formerly been necessary. The diet for diabetic patients has become a very precise and accurate procedure during the last few years, but, unfortunately, many physicians have not been sufficiently trained in this regard. No disorder in metabolism has been more completely

studied than the condition of diabetes, and no subject in medicine has received greater attention from master clinicians; yet the majority of physicians are in a woeful state of ignorance on the subject and, in consequence, the diet prescribed for the majority of diabetic patients is fifty years behind the times. Unless this state of affairs is corrected, insulin will be misused and encounter unjustified disrepute instead of proving the blessing it is.

The chief and most cogent danger from the introduction of insulin is that its manufacture and standardization may not continue to be successfully controlled, and that exploitation of the profession and the public will be practised by unscrupulous peddlers of drugs. The next serious concern is that the physician who is entrusted with insulin will not properly safeguard his patient from the serious hypoglycemic reactions that result when the dose is insufficiently buffered by food. In very rare cases it may be permissible to inject a single dose of insulin without thus buffering it with glucose, but its continued administration must always be accompanied by definite weighed quantities of food of known composition and sugar value.

Careful balancing of the insulin dosage and food involves systematic adjustment of diet, and imposes on the physician the duty of familiarizing himself with precise quantitative methods of dieting, such as have been described in this country by Joslin, Woodyatt, Allen, myself, and others. These methods vary in detail; certain physicians prefer more liberal fat allowances, others insist on more rigorous undernutrition, but the necessity of quantitative control of the food, the avoidance of overfeeding, and the avoidance of acidosis by judicious balancing of the fat and the carbohydrate of the metabolizing food substances, is common to all.

Adams, in the second paper of this series, recapitulates the dietary methods employed in the Mayo Clinic and describes certain charts which simplify the calculation of these diets. The usefulness of these charts has been very considerably augmented by his ingenuity. Barborka, in the third paper, discusses in detail the use of insulin and describes the procedures which have been followed in this Clinic, with, on the whole, satisfactory

results. The purpose in publishing this series of papers is to help in distributing information with regard to the use of insulin, and with regard to our experience with its difficulties and dangers. Our experience is necessarily limited and, in all probability, we shall later revise much that we are doing now. We cannot, therefore, be dogmatic except in emphasizing the importance of precision in using this material.

TRAINING THE PATIENT

In closing, I wish to add a word in regard to the importance of training the patient. The physician's duty is by no means ended when he has succeeded in controlling acidosis and glycosuria, and has established his patient on an adequate diet, properly balanced against the insulin dosage. The patient must be able to follow this diet at home with food scales and tables of food value; furthermore, he must be carefully instructed in the use of insulin, and advised about the emergencies which may arise. How is this to be accomplished? Only by putting the patient through a systematic course of study and drill. This takes time and much patience, but the reward justifies the effort. Unless the patient is able to continue treatment intelligently, his case has not been properly managed. Following Mosenthal, a number of diabetic clinics now provide a systematic course of instruction for their patients. Text-books are employed; charts, models, and other teaching facilities are made use of, and lectures and quizzes are held. There is much to be said in favor of starting treatment in such an institution. A school atmosphere prevails; the patient meets other patients with difficulties similar to his own, he obtains help from them and gives help in return; he works more diligently than he is likely to do alone in his home, and is more thoroughly impressed by the importance of strict adherence to his weighed diet, and to the rules and regulations. On the other hand, such institutional treatment is by no means indispensable. Excellent results may be obtained by properly conducted office consultations, provided the physician is thoroughly familiar with the subject of dietetics, and will recognize the importance of this part of the treatment,

and devote himself untiringly to the task. Now that we have insulin, and that the results of treatment of diabetes have been so materially improved, it is to be hoped that greater efforts will be made in this direction.

Note: References referred to in this series of three papers on diabetes and other references on insulin will be found with the third paper of the series.

FOOD MIXTURES SUITABLE FOR DIABETIC PATIENTS RECEIVING INSULIN AND A METHOD FOR CALCULATING DIETS

S. Franklin Adams

A short survey of the dietary management of diabetes may be helpful at this time because, if insulin is to be used with the success it deserves, the dietetic aspect of the treatment of diabetes must receive most careful consideration. Any tendency, however small, toward carelessness in the planning of the diet cannot help but detract from the value of the remarkable substance placed in the hands of the physician through the brilliant work of Banting and Best.

During the last few years there has been an orderly advance in the field of diabetic dietotherapy. The clinician, the physiologist, and the chemist have joined forces, and as a result of their combined efforts, the frontier of knowledge has been gradually extended, so that now several strong positions have been taken and four main principles have been established.

The first of these principles is that of total dietary restriction. Allen, and Joslin, particularly, have demonstrated the benefit that would accrue from the practice of this tenet. Their teaching is in harmony with the views of prominent clinicans abroad and is interestingly substantiated by the observations of Magnus-Levy made during the war when the people of Berlin were obliged to limit their intake of food. Of late there has been a tendency to disregard the importance of dietary restriction, due no doubt, to a revolt against the extremes of undernutrition that have been practised. While drastic restriction and its sequel, marked loss of body weight, are open to criticism, we must not be influenced by this to the extent of failing to appreciate the importance of a proper limitation of food. The ideal régime

would maintain the body weight at a desirable level while avoiding what has been termed "luxus consumption." In other words, it would limit the food calories to actual needs.

The principal advantage of food restriction probably lies in the resulting depression of the metabolic rate. In 1916 Allen and DuBois indicated that reduction of metabolism in diabetes is desirable, because it results in a less insistent demand for food on the part of the organism. Allen's results with partially depancreatized dogs suggest that the effects of undernutrition are due to a reduction of the metabolism. The beneficial influence of the depression of metabolism is further shown by Wilder, Boothby and Beeler in the report of a case of severe diabetes, thoroughly studied. The metabolism is usually depressed by starvation or protracted undernutrition, but this is not always the case. Extreme undernutrition may elevate the metabolism as Loewi found by observation made on himself during the war period.

The basal metabolic rate in diabetes has proved to be a point of contention. Considerable confusion has arisen because of two factors; first, the method of selection of standards by Benedict and Joslin as shown by Falta and Meyer, Lusk, Murlin and Boothby and Sandiford; second, a large caloric or high protein intake just preceding the study of the metabolism, and causing an increased rate. Joslin, in a recent contribution, indicates that diet and acidosis are the two chief factors governing the metabolic rate. He asserts that prior to June, 1914, which marked the introduction of Allen's undernutrition treatment, the average metabolic rate was 13 per cent above the standard of Harris and Benedict. After June, 1914, it was 7 per cent below this standard, implying that this secondary lower level is a result of the practice of Allen's ideas. Allen and Du Bois observed thirty-six patients with diabetes and found thirteen with normal metabolism, nine above, and four below the Du Bois standard. The findings at the Mayo Clinic have been that the basal metabolic rate of adequately nourished diabetic patients does not exceed the Du Bois normal limits when such factors as infection, hyperthyroidism, high protein or high caloric intake

can be ruled out. We are more inclined to the view that acidosis *per se* does not increase the metabolism, but that the increase which is so commonly observed in patients with acidosis is brought about as a secondary factor by the same agency which is causing the acidosis. Patients with diabetes who are under weight, and who have been on a low protein and low total calorie intake usually have a metabolic rate somewhat below the normal standard of Du Bois. When the metabolic rate of patients is equal to, or higher than, the Du Bois standard it is considered an indication that the patient has received an excessive amount of food, especially protein, or that he is calling on his own tissues to meet his demands and through the exhaustion of fat and carbohydrate stores, is catabolizing large amounts of his body protein.

A depression of the metabolic level of from 15 to 25 per cent may be occasioned, and the chief benefit of dietary restriction may be secured in most cases by feeding diets of a caloric value between the basal needs of the patient and 20 per cent below this, depending on the severity of the case, and calculated from the patient's height, weight, age and sex. A diet thus planned will be balanced by a depression of the metabolism and, in a short time, the patient will attain an equilibrium with only a moderate loss of weight, provided but slight exercise is permitted. This régime has been termed "low maintenance," as against "undernutrition." When undernutrition is practised, according to Allen and Joslin, the food restriction is far more rigorous.

The second principle is that of protein restriction. It is recognized that 58 per cent of the protein of the diet can be used as glucose by the organism. Furthermore, because of its specific dynamic action, protein causes an increase in the metabolism. Moreover, protein in excess embarrasses the organism in its attempt to utilize glucose. The importance of these facts has been emphasized. The feeding of protein should be done with the nitrogen balance constantly in mind. It has been found in treating diabetes at the Clinic, that two-thirds of a gram of protein for each kilogram of body weight for twenty-four hours usually maintains the patient in nitrogen equilibrium. Children,

as a rule, require 1 gm. of protein for each kilogram of body weight.

The feeding of this amount of protein approximates the method of treatment of Marsh, Newburgh and Holly. These investigators have shown, in an inquiry into the protein requirements of diabetic patients, that the nitrogen balance may be established according to laws which govern the nondiabetic individual, if the total caloric demand is satisfied. It is largely due to an appreciation of the value of protein restriction that Newburgh and March have obtained such good results with the high fat diets which they propose.

The third principle to be considered is that of carbohydrate restriction. It is evident that an enfeebled carbohydrate mechanism should be treated with the utmost consideration and that the carbohydrate should be rigorously restricted. There is abundant clinical evidence to support this view. Woodyatt considers "that a weakened pancreas, in the presence of a sufficient supply of glucose, might be stimulated into a state of fatigue and decreased function, and that a sufficient diminution of the glucose supply might then lessen the stimulation, place the organ in a state of comparative rest, and permit it to recuperate up to a certain limit." Such a view, as he says, affords an explanation of many observed facts. It seems logical, therefore, to give only the amount of carbohydrate which is sufficient to balance safely the ketogenic effect of the fatty acids.

The fourth principle is that of balancing the ketogenic (fatty acid) and the antiketogenic (glucose) materials in a food mixture. When a disproportionate amount of fat or ketogenic material is utilized by the organism, the forerunners of acidosis make their appearance. Coma appears if this disproportion is allowed to continue unchecked. Woodyatt, for many years, consistently opposed the view introduced by Allen that fat must be rigorously restricted in diabetic diets, and his opinion and wide clinical experience, together with the excellent therapeutic results obtained by Newburgh and Marsh with unusually high fat diets, have to a large extent dispelled the fear of fat that was formerly held by many clinicians. Several years ago, Woodyatt

proposed that a molecular relationship or ratio between fatty acids and glucose governed the oxidation of fat in the body. The chemical studies of Shaffer have shown that this is the case, and thus may be explained the degree of safety of high fat diets when some such systematic procedure is followed as is advocated herewith. Shaffer has found by experiments conducted in the chemical laboratory that every two molecules of ketogenic material (aceto-acetic acid), require for their complete oxidation with hydrogen peroxid the association of one molecule of glucose. Wilder and Winter, in clinical studies, obtained the same ratio between the calculated ketogenic molecules of the metabolizing food substances, and the molecules of metabolizing glucose; that is to say, a ratio of two molecules of fatty acids to one molecule of glucose.

These important facts definitely establish the limit of safety in fat feeding, provided the nitrogen and caloric requirements of the patient are taken into account. The latter must not be disregarded. If the diet does not dovetail with the demands of the organism, the endogenous food supply will be called on, endogenous fat will enter the metabolism, and acidosis will follow. It is of vital importance, therefore, to calculate the caloric demand as accurately as present knowledge will permit, and knowing this demand, to supply food calories in sufficient number to satisfy it. Several factors, principally infection, affect the metabolism unfavorably and predispose to acidosis. Therefore, in planning diets, a margin of safety should be allowed in the ratio between the ketogenic and antiketogenic substances.

About a year ago a system of planning diets was described by Wilder which included all of the principles discussed here, namely, a lowering of the metabolic rate without loss of body tissue, low protein, low carbohydrate, and a safe ratio between the ketogenic and antiketogenic substances. These principles have guided our treatment for two years and the therapeutic results obtained with the proposed low maintenance diets have been very satisfactory. In all except the severest cases, the glycosuria and acidosis of the patients admitted to the hospital have been promptly controlled, and it has at times been possible

to succeed by this method when starvation or more rigorous restriction of diet was unavailing. It must be remembered that rest in bed is necessary, and in many cases it has been found advantageous to interpolate an occasional single day of complete fast. If at the end of three days the urine still shows sugar this procedure is instituted routinely to hasten the desugarization of the patient. When the patient is allowed out of bed, the calories are increased 20 to 30 per cent, depending on the amount of physical exertion to be permitted.

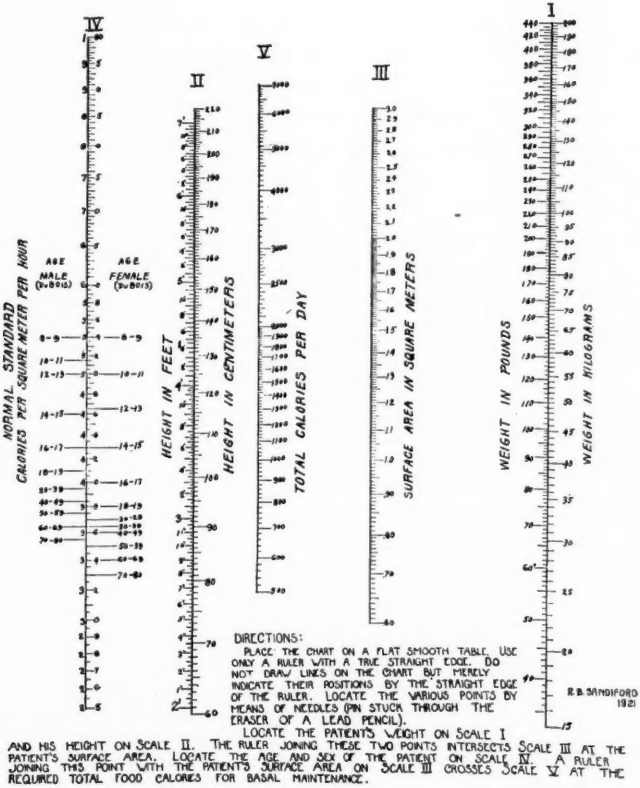
The introduction of insulin implies the use of larger allowances of food than those described when this system of diets was introduced, and may modify the necessity for such rigorous restriction of protein as has been advocated. Nevertheless the general principles still hold, and the economical use of the improved tolerance which a given dosage of insulin accomplishes involves the planning of diets along lines similar to those here discussed. Furthermore, it is desirable to determine the original glucose tolerance of the patient before starting insulin treatment, and it has been found advantageous to begin treatment with the standard low maintenance diet described in making such determinations. For these reasons the charts for calculating the diets suggested by Wilder will be explained, and a modification of one of these charts proposed by the writer will be described.*

The first step in the calculation of the low maintenance diet is to determine the daily food calories required for the resting patient, the age and sex, height and weight being known. This is accomplished with Chart 1 as explained by the directions appearing thereon. Chart 2 gives the distribution of the carbohydrate, protein, and fat in the diet, when the total calories are known, and when one of these food substances is fixed. The protein is the one usually fixed and as a rule 0.66 gm. of protein are permitted for each kilogram of body weight during the preliminary period when tolerance is being determined. Diets thus calculated have a ketogenic ratio of 1.65 : 1, thus avoiding the 2 : 1 or threshold ratio by a small margin.

* These charts can be obtained from W. B. Saunders Co., West Washington Square, Philadelphia, or from H. N. Elmer, 1641 Monadnock Building, Chicago.

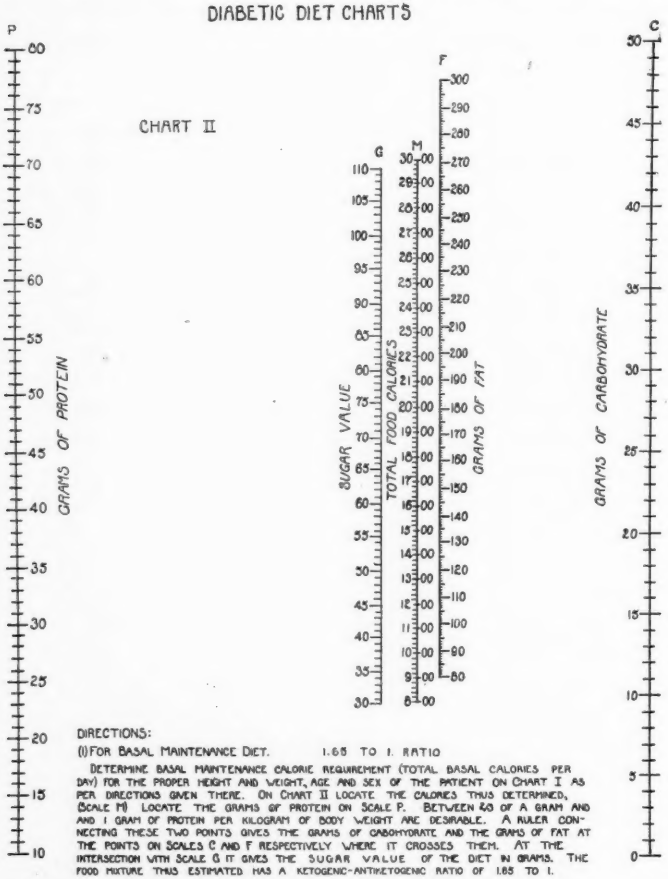
It occurred to me that the usefulness of Chart 2 would be enhanced by incorporating a scale which would give the sugar value of the diets, as calculated by Woodyatt's formula G= 0.58 P+0.10 F+C. The sugar value or glucose equivalent is

CHART I.


IV
II
V
III
I
NORMAL STANDARD CALORIES PER SQUARE METER PER HOUR
AGE MALE (DuBOIS)
AGE FEMALE (DuBOIS)
HEIGHT IN FEET
HEIGHT IN CENTIMETERS
TOTAL CALORIES PER DAY
SURFACE AREA IN SQUARE METERS
WEIGHT IN POUNDS
WEIGHT IN KILOGRAMS
DIRECTIONS:
PLACE THE CHART ON A FLAT SMOOTH TABLE. USE ONLY A RULER WITH A TRUE STRAIGHT EDGE. DO NOT DRAW LINES ON THE CHART BUT MERELY INDICATE THEIR POSITIONS BY THE STRAIGHT EDGE OF THE RULER. LOCATE THE VARIOUS POINTS BY MEANS OF NEEDLES (PIN STUCK THROUGH THE ERASER OF A LEAD PENCIL).
LOCATE THE PATIENT'S WEIGHT ON SCALE I AND HIS HEIGHT ON SCALE II. THE RULER JOINING THESE TWO POINTS INTERSECTS SCALE III AT THE PATIENT'S SURFACE AREA. LOCATE THE AGE AND SEX OF THE PATIENT ON SCALE IV. A RULER JOINING THIS POINT WITH THE PATIENT'S SURFACE AREA ON SCALE III CROSSES SCALE V AT THE REQUIRED TOTAL FOOD CALORIES FOR BASAL MAINTENANCE.
R.B. SANDIFORD 1921

the amount of sugar available to the organism in the course of the metabolism of a given food mixture, and is considered to consist of 58 per cent of the weight of the protein, 10 per cent (the glycerole fraction) of the fat, and 100 per cent of the carbohydrate contained in the food mixture. It is especially impor-

tant to know this sugar value in planning the increased diets for use with insulin. Accordingly the original chart was re-


DIABETIC DIET CHART 5
CHART II
P
GRAMS OF PROTEIN
G
SUGAR VALUE
M
TOTAL FOOD CALORIES
F
GRAMS OF FAT
C
GRAMS OF CARBOHYDRATE
DIRECTIONS:
(1) FOR BASAL MAINTENANCE DIET. 1.65 TO 1. RATIO
DETERMINE BASAL MAINTENANCE CALORIE REQUIREMENT (TOTAL BASAL CALORIES PER DAY) FOR THE PROPER HEIGHT AND WEIGHT, AGE AND SEX OF THE PATIENT ON CHART I AS PER DIRECTIONS GIVEN THERE. ON CHART II LOCATE THE CALORIES THUS DETERMINED, (SCALE M) LOCATE THE GRAMS OF PROTEIN ON SCALE P. BETWEEN 45 OF A GRAM AND AND 1 GRAM OF PROTEIN PER KILOGRAM OF BODY WEIGHT ARE DESIRABLE. A RULER CONNECTING THESE TWO POINTS GIVES THE GRAMS OF CARBOHYDRATE AND THE GRAMS OF FAT AT THE POINTS ON SCALES C AND F RESPECTIVELY WHERE IT CROSSES THEM. AT THE INTERSECTION WITH SCALE G IT GIVES THE SUGAR VALUE OF THE DIET IN GRAMS. THE FOOD MIXTURE THUS ESTIMATED HAS A KETOGENIC-ANTIKETOGENIC RATIO OF 1.65 TO 1.
(2) FOR MAXIMUM CALORIE DIET (INSULIN).
HAVING DETERMINED ON SCALE G THE SUGAR VALUE OF THE BASAL MAINTENANCE DIET, ADD THE NUMBER OF GRAMS OF GLUCOSE TO BE BALANCED BY INSULIN. LOCATE THIS VALUE ON SCALE G. ANY STRAIGHT LINE INTERSECTING SCALE G AT THIS POINT AND CROSSING THE OTHER SCALES WILL GIVE A DIET THAT HAS A KETOGENIC-ANTIKETOGENIC RATIO OF 1.65 TO 1.

constructed and a glucose scale incorporated (Chart 2). The new chart permits us with one setting of a ruler connecting the two points, total calories and protein grams, to read off not

only the fat grams and carbohydrate grams, as in Wilder's original chart, but also the sugar value of the diet. Let us say, for example, that the glucose tolerance of a given patient is 30, and that as the result of a larger glucose capacity from insulin we desire to increase the glucose value of the food mixture by 50 and still retain the desired aketogenic proportions of the former diet; we have merely to advance the point on the sugar value scale up to the new value 80 and any line passing through this point will give an aketogenic diet out of which it is possible for the patient to metabolize 80 gm. of glucose.

Diabetic patients are likely to find an unchanged diet monotonous if they are required to use it for any considerable period, and the use of insulin should afford greater latitude in diet than was permissible formerly. The new scale will serve to vary the monotony of the diet because, if the point on the sugar value scale is taken as a pivot, the diet can be changed from low protein and high carbohydrate content to higher protein and lower carbohydrate content with but little change in the fats and a negligible change in total calories. It is to be remembered in this connection, however, that high protein diets are to be used with caution.

Occasionally it may be desirable to plan a diet in which the ketogenic and antiketogenic substances are in a lower ratio than that given by the chart. This can be accomplished without very materially affecting the total calories by arbitrarily adding to the carbohydrate. It has been determined for instance that the 1 : 1 ratio proposed by Woodyatt can be obtained with reasonable accuracy by multiplying the carbohydrate value read by the factor 2.8, leaving the protein and fat figures unchanged.

It not infrequently happens when diets are planned for patients with tolerance augmented by insulin that the total calories are higher than is desirable. In that case some of the fat may be arbitrarily omitted. Chart 2 gives the most economical distribution of the permissible food glucose, but in cases with a high tolerance in which insulin is being given, such extreme economy may not be necessary.

CONSTRUCTION OF NOMOGRAPHIC CHART FOR COMPUTING DIETS

The calculations by means of which Wilder was able to set his scales have been changed in Chart 2 and therefore the new calculations are given here (Table 1). The two formulas derived by Wilder for computing his low carbohydrate antiketogenic food mixtures are:

$$(1)\ C = 0.024\ M - 0.41\ P.$$
$$(2)\ F = 4\ C + 1.4\ P.$$

In order to calculate a value for glucose with reference to these equations, Woodyatt's formula was employed:

$$(3)\ G = 0.58\ P + 0.10\ F + C.$$

The value for F in Formula 2 was substituted in Formula 3, and this, in its simplest form, gives Formula 4:

$$(4)\ G = 0.72\ P + 1.4\ C.$$

The directions of Lipka, Boothby and Sandiford, and Wilder, were followed in the construction of this nomographic chart. It will be seen that there are three unknown factors in each of the three equations. Two of the factors, C and P, appear in all of the three equations. The scale for C can be of such length that it will satisfy all of the equations, provided a suitable modulus is chosen in each instance. This also holds true for Scale P. Thus, when two of the five variable factors are known, one setting will solve the equation and give values for M, F and G. Table 1 illustrates the manner in which the scale lengths were determined. The distance between the Scales

Table 1 *

Scale	Limits	Modulus	Scale equation	Scale length
C Difference	50 gm. f1 (4C) = 200 0 f1 (C) = 50 50 f1 (1.4C) = 70	m1 = 1 mm. m1 = 4 mm. m1 = 2.86 mm.	x = m1f1 x = m1f1 x = m1f1	1 x 200 = 200 mm. 4 x 50 = 200 mm. 2.86 x 70 = 200 mm.
P Difference	80 gm. f2 (1.4P) = 98 10 f2 (0.41P) = 28.7 70 f2 (0.72P) = 50.4	m2 = 2 mm. m2 = 6.83 mm. m2 = 3.88 mm.	y = m2f2 y = m2f2 y = m2f2	2 x 98 = 196 mm. 6.83 x 28.7 = 196 mm. 3.88 x 50.4 = 196 mm.
F Difference	300 gm. f3 (F) = 220 80 220	$m3 = \frac{m1 \times m2}{m1 + m2}$ $\frac{1 \times 2}{1 + 2} = 0.66$ mm.	z = m3f3	0.66 x 220 = 145.2 mm.
M 3,000 cal. f3 (0.024M) = 52.8 Difference	800 2,200	$m3 = \frac{m1 \times m2}{m1 + m2}$ $\frac{4 \times 6.83}{4 + 6.83} = 2.51$ mm.	z = m3f3	2.51 x 52.8 = 133.1 mm.
G Difference	110 gm. f4 (G) = 80 30 80	$m4 = \frac{m1 \times m2}{m1 + m2}$ $\frac{2.86 \times 3.88}{2.86 + 3.88} = 1.63$ mm.	s = m4f4	1.65 x 80 = 130 mm.

*Chart 2 as reproduced does not conform to the measurements given in this table. These measurements refer to the original chart.

C and P is 160 mm. A line bisecting scale P also bisects scale C. These two scales were charted and graduated. All graduations are *uniform*. Therefore, the protein scale P was divided into 70 equal parts with limits of 80 and 10. The carbohydrate scale C was divided into 50 equal parts, with limits of 50 and 0.

The next step was to calculate the position of the fat scale, and this was accomplished by means of the following equations:

$$\begin{aligned} &pc = pf + fc = 160 \text{ mm.} \\ &pf : fc = m2 : m1 = 2/1 \\ \therefore\ &pf = 2\,fc \end{aligned}$$

and

$$\begin{aligned} &pf = 160 - fc \\ \therefore\ &2\,fc + fc = 160 \text{ mm.} \\ &3\,fc = 160 \text{ mm.} \\ &fc = 160/3 = 53.3 \end{aligned}$$

The fat scale F was therefore placed 53.3 mm. from scale C. Since $F = 4C + 1.4\,P$, the point 80 on the F scale can be readily found by connecting the point 10 on scale P with the point 16.5 on scale C. It is then possible to graduate scale F from 80, which is its lower limit, to 300, which is its upper limit. The next step was to determine the position of the calorie scale M and this was accomplished by means of the following equations:

$$\begin{aligned} &pc = pm + mc = 160 \text{ mm.} \\ &pm : mc = m2 : m1 = 6.83/4 \\ \therefore\ &pm = 6.83\,mc/4 = 1.71\,mc. \end{aligned}$$

and

$$\begin{aligned} &pm = 160 - mc \\ \therefore\ &1.71\,mc + mc = 160 \text{ mm.} \\ &2.71\,mc = 160 \text{ mm.} \\ &mc = 160/2.71 = 59.0 \text{ mm.} \end{aligned}$$

Scale M was therefore charted 59 mm. from scale C. According to the formula $C = 0.024M - 0.41\,P$, the point 800 on the M scale can be found by connecting the point 10 on scale P with the point 15.1 on scale C. It was then possible to graduate scale M from 800 which is its lower limit, to 3000 which is its upper limit.

The final step was to calculate the position of the sugar value scale G, and this was done by employing the following equations:

$$\begin{aligned} &pc = pg + gc = 160 \text{ mm.} \\ &pg : gc = m2 : m1 = 3.88/2.86 \\ \therefore\ &pg = 3.88\,gc/2.86 = 1.36\,gc \end{aligned}$$

and

$$\begin{aligned} \therefore\ &pg = 160 - gc \\ &1.36\,gc + gc = 160 \\ &2.36\,gc = 160 \\ &gc = 160/2.36 = 67.8 \end{aligned}$$

Scale G was therefore charted 67.8 mm. from scale C. According to the formula $G = 0.72\ P + 1.4\ C$, the point 30 on the G scale can be found by connecting the point 10 on scale P with the point 16.3 on scale C. Scale G was then graduated from its lower limit which is 30, to its upper limit which is 110.

SUMMARY

Several important considerations regarding dietotherapy for diabetic patients are reviewed. A system of diets is described which has taken these considerations into account.

A modification of the nomographic chart for the calculation of low maintenance diets for diabetic patients is described. A new scale has been introduced by means of which it is possible to determine the sugar value of the diets.

This chart has the advantage of being a simple and accurate means of determining, by the single setting of a straight-edge, the amount of fat, carbohydrate, and protein of an aketogenic diet, its total calories, and sugar value, when any two of these five variables are known and fixed.

USE OF INSULIN IN THE TREATMENT OF DIABETES

CLIFFORD J. BARBORKA

IN the preceding papers by Wilder and Adams, the clinical results from treatment with insulin, the indications for the use of insulin, the principles governing the dietary management of the patient, and the technic of planning suitably proportioned diets, are considered. The present discussion, therefore, will be limited to a description of the actual procedures now employed in the Mayo Clinic in the treatment of patients requiring insulin. The methods in other clinics differ from ours in a number of particulars, and may be obtained by consulting the articles listed in the appended bibliography.

The course of treatment in the Mayo Clinic requires from four to eight weeks, depending on the severity of the case, and the intelligence of the patient. Glycosuria and acidosis may be controlled in a few days, and an estimate of the patient's tolerance, and his insulin dosage and food requirement, is usually determined within ten days or two weeks. The balance of the period of hospitalization is taken up in the treatment of complications, such as chronic infection of the teeth and tonsils, and other possible foci, and, particularly, in the training of the patient. Such training is believed to be of vital importance for the successful continuation of the treatment, and consists of a systematic course of instruction by means of lectures, demonstrations, and quizzes. The instruction covers the computing of diets, the qualitative analysis of the urine for sugar and acetoacetic acid, and the technic of the hypodermic injection of insulin. The patient is also taught how to meet certain emergencies that may be anticipated. For example, should his supply of insulin be interrupted for any cause, his intake of food must be cut down immediately; he must return to his basal maintenance diet, and remain in bed until the insulin is resumed.

He must also learn how to recognize the symptoms of hypoglycemia and be prepared to combat them promptly, and know what to do if complicating infections intervene. In the cases of children, one of the parents is instructed.

While the patient is in the hospital, every effort is made to establish satisfactory coöperation with his family physician. In case the physician has had no experience with insulin, he is given the necessary directions for the subsequent management of the case. The patient takes with him to his home a ten days' supply of insulin, and arrangements are made with the manufacturer to send to the family physician regular allotments at bimonthly or monthly intervals. The necessity of consulting a physician professionally at monthly intervals is impressed on the patient.

When a new patient is admitted to the hospital with urine strongly positive, for sugar and aceto-acetic acid, and coma may be threatening. It is a rule, therefore, to put every new patient to bed at once, to give a cleansing enema and ample fluids, and to limit the food for the day of admission to 100 gm. of orange juice every six hours. If the physical examination does not reveal contraindications, one of the procedures illustrated in Tables 1, 2, and 3 is instituted, beginning on the morning of the second day.

PROCEDURE IN SIMPLE CASES

In Table 1 is the summary of the dietary manipulation of a typical uncomplicated and easily managed case. This patient (Case A420437) was a man 5 feet 9 inches in height, aged thirty-two years, who had had diabetes for two years and three months. The onset of the disease had been acute with the typical cardinal symptoms of diabetes, and the body weight had fallen from 215 to 146 pounds. The progress of the disease had been fairly successfully controlled by qualitative restriction of the diet until four months before, when symptoms recurred, and glycosuria was prevented with difficulty. The sugar and aceto-acetic acid reactions of the urine were strongly positive. On the morning after admission to the hospital the blood contained 321 mg. of sugar for each 100 c.c., and the plasma dioxid combining power

Table 1

Case A420437. A man, aged thirty-two years, weight 146½ pounds; height 5 feet, 9 inches.

Basal maintenance diet: Carbohydrate 23 gm., protein 44 gm., fat 153 gm., calories 1700

	Days	1*	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	Average sugar value of metabolizing food of test period, days 12, 13, and 14
Diet	Carbohydrate	10	23	23	23	Fast	11.6	23	23	23	43	43	63	63	63	74	74	74	From carbohydrate = 63 gm.
	Protein		44	44	44		22	44	44	44	44	44	44	44	44	66	66	66	From protein (urine nitrogen x 3.7) = 36.1 gm.
	Fat		153	153	153		76.5	153	153	153	153	153	153	153	153	220	220	220	
	Sugar value	Orange juice	63.8				31.9	63.8			83.8		103.8			134.8			From fat 153 ÷ 10 = 15.3 gm.
	Total calories		1700	1700	1700		850	1700	1700	1780	1780	1780	1860	1860	1860	2620	2620	2620	Total =114.4 gm.
													Test period						Glucose excretion - 0 gm.
																			Tolerance =114.4 gm.
Urine, 24 hours	Sugar, gm.	+	56	55	55	12.2	10.3	8.4	Faint trace	0	0	0	Trace	Trace	Trace	Trace	Trace	0	10 units of insulin will permit a diet with a sugar value of 114.4 + 20 = 134 gm.
	Gerhardt test	+	+	+	?	Trace	0	0	0	0	0	0	0	0	0	0	0	0	
	Nitrogen, gm.								12.47		9.13	9.61	9.68	9.98	9.60	7.9	7.66		Insulin diet: C74, P66, F220, Calories 2620
Blood	Blood sugar, mg. for each 100 c.c.		0.321													Insulin 10 units, #779	10 units #779	10 units #768	
	Blood plasma, carbon dioxid, volume per cent		40																

*On the day of admission only orange juice is given for food. The day is incomplete, the patient usually being admitted to the hospital in the afternoon.

was 40 volumes per cent. The basal maintenance diet for this patient, as calculated by our formulas with the aid of the chart described by Adams in the preceding lecture, was 1700 calories, distributed as 23 gm. of carbohydrate, 44 gm. of protein, and 153 gm. of fat. This diet was instituted on the morning of the second day, but failed to control the glycosuria and aceto-acetic acid excretion in three days. On the fifth day, therefore, no food was allowed, and on the sixth day half diet was given, returning then to the basal maintenance allowance, with the result that the glycosuria and acidosis were controlled. On the tenth day the diet was increased by 20 gm. of carbohydrate for the purpose of determining the patient's tolerance. The urine remained sugar free, and, on the twelfth day, 20 gm. of carbohydrate were again added. For the next three days a very small constant trace of sugar was excreted daily. The food allowance for this period was therefore taken as representing the patient's maximal tolerance, and, the nitrogen excretion being known, an estimate of the sugar value of the metabolizing foods was made, thus making it possible to assign a numerical value to the patient's tolerance. The calculation is illustrated in Table 1. The sugar value of the metabolizing foods is computed as suggested by Woodyatt, and is based on the assumption that all of the carbohydrate, 58 per cent of the protein, and 10 per cent of the fat are convertible to glucose. Many diabetic patients have negative nitrogen balances. For this reason it is more accurate to estimate the sugar from protein by determining the number of grams of nitrogen excreted each day, and by multiplying this by the factor 3.7 (Table 1).

The calculation revealed that this patient had a very fair tolerance, 114 gm. In general, a tolerance above 100 gm. permits the allowance of a diet of 2500 or more calories, provided these are suitably distributed to fat, protein, and carbohydrate. It might seem, therefore, that this patient did not require insulin, but we believe that it is usually advisable to give insulin in a progressive case of this type, if for no other reason than because the insulin tends to check what otherwise may be a negative nitrogen balance. For such purposes, however, a small dose is

usually sufficient; in the case under discussion, a dose of 10 units was decided on. The additional glucose tolerance provided by each unit of insulin is usually about 2 gm. Ten units should permit, therefore, a diet with a sugar value 20 gm. higher than the patient's tolerance, namely, 134 gm. A diet was planned, as described by Adams, and a food allowance of 2620 calories distributed as 74 gm. of carbohydrate, 66 gm. of protein, and 220 gm. of fat was decided on. On the fifteenth day this higher diet was started and the injections of insulin were begun. As predicted, the régime was tolerated perfectly.

If the original tolerance of the patient can be determined in this manner, and insulin dosage is planned accordingly, further manipulation of either the diet or insulin dosage is usually unnecessary unless the patient's own contribution of pancreatic hormone should change. However, in many cases, especially those of relatively early diabetes, the pancreatic function may improve and the rising tolerance makes it necessary, later, either to reduce the dose of insulin, or to increase the carbohydrate quota of the diet. Our practice is not to alter the insulin dose, but to add carbohydrate, a few grams at a time, as becomes necessary.

Table 2 illustrates the procedure with a patient who proved refractory on the routine dietary management, and yet whose acidosis was not so alarming as to prohibit the routine procedure. It is worthy of note that the glycosuria in this severe case was appreciably less intense during the first three days of treatment than that of the preceding, comparatively mild case.

The patient (Case A418346), a woman aged forty years, 4 feet, 10 inches in height, had had diabetes for nineteen months. The onset of the disease had been acute, with the typical cardinal symptoms of diabetes, and the body weight had fallen from 124 to 92 pounds. On admission to the hospital the carbon dioxid combining power of the plasma was reduced to 37 volumes per cent, but since there were no alarming clinical symptoms of acidosis, the routine procedure was instituted at once. The patient's urine did not become clear even after the institution of a fast on the fifth day; nevertheless, as is shown in Table 2,

Table 2

Case A418346. A woman, aged forty years, weight 92 pounds; height 4 feet, 10 inches.

Basal maintenance diet: Carbohydrate 15 gm., protein 27 gm., fat 99 gm., calories 1100

	Days	1*	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Diet	Carbohydrate	10	15	15	15	Fast	7.5	15	15	15	15	15	15	43	43	43	43
	Protein	Orange juice	27	27	27		13.5	27	27	27	27	27	27	45	45	45	45
	Fat		99	99	99		49.5	99	99	99	99	99	99	235	235	235	235
	Sugar value		40.5				20.3	40.5						92.6			
	Total calories		1100	1100	1100		550	1100	1100	1100	1100	1100	1100	2560	2560	2560	2560
									Test period								
Urine, 24 hours	Sugar, gm.	+	25.4	16.3	17.5	7.75	7.2	8.32	8.7	7.2	7.8	8.5	6.2	4.68	7.0	12.5	11.2
	Gerhardt test	+	+	+	+	Trace	0	Trace	0	Trace	Trace	Trace	0	Trace	0	0	0
	Nitrogen, gm.				5.93	7.63		4.48	4.32	4.13	3.81	4.34	4.14		4.42	5.26	5.69
Blood	Blood sugar, mg. for each 100 c.c.		0.232											Insulin 30 units #753	30 units #753	30 units #758	30 units #758
	Blood plasma, carbon dioxid volume per cent		37														

Average sugar value of metabolizing food of test period, days 8, 9, 10, 11, and 12

From carbohydrate	=15 gm.
From protein (urine nitrogen x 3.7)	=15.5 gm.
From fat 99 ÷ 10	= 9.9 gm.
Total	40.4 gm.
Glucose excretion	- 7.2 gm.
Tolerance	= 33.2 gm.

30 units of insulin will permit a diet with a sugar value of 33.2 ÷ 60 = 93.2 gm.

Insulin diet: C43, P45, F235, calories 2560

*On the day of admission only orange juice is given for food. The day is incomplete, the patient usually being admitted to the hospital in the afternoon.

a constant excretion of sugar was obtained in the period from the eighth to the twelfth day, and the tolerance could be determined by subtracting the daily number of grams of glucose excreted from the sugar value of the metabolizing foods. This gave a tolerance of 33 gm., and it was decided to make the dose of insulin 30 units, which would permit a diet with a sugar value of 93, or an allowance of 2560 calories, distributed as 43 gm. of carbohydrate, 45 gm. of protein, and 235 gm. of fat. As may be noted in Table 2 the treatment was tolerated almost as predicted.

Table 3 illustrates the management of a patient with reasonably severe acidosis, requiring the immediate administration of insulin in order to avoid the danger of coma. In such cases the estimation of tolerance is postponed until the patient is well out of danger.

The patient (Case A420392), a girl aged twenty-three years, 5 feet, 4 inches in height, had had diabetes for five months. The onset had been acute, following immediately on the shock of losing a brother by drowning. The body weight had fallen from 125 to 95 pounds. Accurate treatment was instituted early in another clinic, and a weighed diet, consisting of 73 gm. of carbohydrate, 85 gm. of protein, and 156 gm. of fat, had been well tolerated until one month before admission to the Mayo Clinic, when glycosuria had recurred. The patient, becoming discouraged, had broken her diet two weeks before, and had eaten unrestrictedly. On examination there were no clinical symptoms of impending coma, other than considerable dehydration, but the dry tongue and a plasma carbon dioxid combining power of 25 volumes per cent prompted the immediate administration of insulin in 20 unit doses, the patient receiving her calculated basal maintenance diet. This treatment was continued until the seventh day, when the insulin was stopped, and during the following three-day period the tolerance was estimated as being 37.5. It was predicted that 30 units of insulin would permit a diet with a sugar value of 97.5, and such a régime was started on the eleventh day. It was tolerated as predicted.

Table 3

Case A420392. A woman, aged twenty-three years, weight 95½ pounds; height 5 feet, 4½ inches.

Basal maintenance diet: Carbohydrate 19 gm., protein 28 gm., fat 115 gm., calories 1260

	Days	1*	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Diet	Carbohydrate	20	19	19	19	19	19	19	19	19	19	50.5	50.5	50.5	50.5	50.5	50.5
	Protein		28	28	28	28	28	28	28	28	28	43	43	43	43	43	43
	Fat		115	115	115	115	115	115	115	115	115	220	220	220	220	220	220
	Sugar value	Orange juice	46.7									97.4					
	Total calories		1260	1260	1260	1260	1260	1260	1260	1260	1260	2429	2429	2429	2429	2429	2429
								Test period									
Urine 24 hours	Sugar, gm.	+	28.1	Trace	Trace	Trace	0	25.7	18.0	15.1	Lost	15.4	15.7	9.6	0	7.2	0
	Gerhardt test	+	+	+	+	Trace	Trace	+	+	+	+	+	+	+	Trace	Trace	0
	Nitrogen, gm.						4.6	8.57	6.38	6.62		6.84	6.35	3.88	4.12	3.18	
Blood	Blood sugar, mg. for each 100 c.c.		0.259														
	Blood plasma, carbon dioxid, volume, per cent		25	37													
	Insulin	20 units #775	20 units #775	20 units #775	20 units #775	20 units #775	20 units #775	Stopped				30 units #774	30 units #774	30 units #774	30 units #479	30 units #479	30 units #479

Average sugar value of metabolizing food of test period, days 7, 8, and 9

From carbohydrate = 19 gm.

From protein (urine nitrogen x 3.7) = 26.6 gm.

From fat 115 ÷ 10 = 11.5 gm.

Total = 57.1 gm.

Glucose excretion − 19.6 gm.

Tolerance = 37.5 gm.

30 units of insulin will permit a diet with a sugar value of 37.5 + 60 = 97.5 gm.

Insulin diet: C50, P43, F220

Calories 2429

*On the day of admission only orange juice is given for food. The day is incomplete, the patient usually being admitted to the hospital in the afternoon.

For children more than ten years of age the procedure as described for adults is applied. For younger children no satisfactory standards are available for determining either basal maintenance diets or caloric requirements at play. One boy, aged three years, with severe diabetes, on a diet of 1340 calories, distributed as 50 gm. of carbohydrate, 50 gm. of protein and 100 gm. of fat, is receiving 20 units of insulin daily; 15 units are administered at 8:00 a.m., and 5 units at 3:00 p.m. He has been excreting about 30 gm. of sugar a day, which is admittedly unsatisfactory. In general, it would seem that young children require at least one-half the food allowance of average adults, with relatively larger proportions of carbohydrate and protein; likewise, they seem to require about one-half the dose of insulin necessary for adults with diabetes of equal severity. In the severest cases, therefore, 20 units a day are given and in the milder cases from 8 to 12 units. Because of the peculiar susceptibility of children to acidosis, and the fact that their blood volume being low, their blood sugar often drops precipitately after administration of insulin, it is much more difficult to balance food and insulin with children than is the case with adults. The younger children undoubtedly present the most difficult of all the insulin problems encountered.

HYPOGLYCEMIA AND REACTIONS FROM INSULIN

In the experimental period when methods of manufacture were under development, reactions attributable to foreign protein were sometimes encountered following injections of insulin. These reactions consisted, in a few cases, of vasomotor disturbances, urticaria, nausea, purging and profuse sweating. Occasionally, also, there were disturbing local reactions, and even sterile abscesses, and ulceration. The insulin received since the first of February, 1923, has not caused such trouble.

The true insulin reaction is due to hypoglycemia and occurs usually two or three hours after injection, the time depending on the blood sugar level and the sugar value of the food taken at the time the injection is made. In an experiment performed with one of the staff of the Clinic as the subject, a reaction was

obtained within thirty minutes. The subject received 30 units of insulin and no food, and his blood sugar at the time of injection was 90 mg. for each 100 c.c. The typical reaction is initiated by weakness and drowsiness, followed by muscular tremors, perspiration, hyperpnea, tachycardia, with full, bounding pulses, and occasional delirium. Recovery at this stage may be spontaneous; otherwise, unless restorative measures are instituted, convulsions, coma, and death supervene. The development of a complete reaction from the time of the initial symptoms takes twenty or more minutes. The blood sugar level during the reaction may be as low as 25 mg. for each 100 c.c. of blood, but usually very definite symptoms appear when it has fallen to 60 milligrams.

Fortunately, the antidote for this hypoglycemia is very simple and effective. A few grams of sugar will control the symptoms almost immediately. Orange juice, glucose, cane-sugar, molasses, honey, and even milk are effective. Our usual practice is to use 100 gm. of orange juice; this contains about 10 gm. of glucose and fructose, and its effect is very prompt. It is not necessary and, therefore, not advisable to use more than 10 or 20 gm. of carbohydrate. If the reaction returns, a second dose of carbohydrate may be given later. If complete coma has developed, glucose can be given by rectum, or epinephrin may be injected subcutaneously. Epinephrin causes mobilization of sugar from the glycogen stores of the liver, and thus antidotes the hypoglycemia. The dose recommended for an adult is 1 mg. (1 c.c. of 1 : 1000 adrenalin); for a child, 0.5 mg. (0.5 c.c. of 1 : 1000 adrenalin). It must be followed by sugar as soon as possible, otherwise all reservations of sugar may be exhausted, and thus a more intense hypoglycemia be provoked. As a last resort, if other measures fail, pure sterile glucose solutions may be injected intravenously.

It is of the utmost importance that the patient be instructed with regard to the symptoms of hypoglycemia, and for this purpose he should be allowed to experience one or two typical reactions while he is under supervision in the hospital. It is also important that he carry on his person some form of sugar

for use in such emergencies. In order that this sugar may not be too tempting, gelatin capsules have been provided, each containing 2 gm. of glucose, five capsules being a dose.

Slight reactions, such as weakness and drowsiness, are fairly common with well-treated patients, and as they occur usually just at mealtime, if arrangements are properly ordered, they are promptly relieved by the meal. Severe reactions are rare. Two instances were observed in the Clinic. A boy, aged three years, developed hypoglycemia when asleep and, hence, by the time attention was obtained, he was already comatose. However, he was able to swallow a dose of orange juice, which restored him promptly. The other case was that of a child with pneumonia and empyema complicating severe diabetes. An overdose of insulin was given preliminary to aspiration of the chest, and the symptoms of hypoglycemia were not recognized as such until the child was comatose. One-half milligram of epinephrin was injected subcutaneously, and repeated in fifteen minutes. Sugar could then be administered by mouth, and restoration followed.

TIME AND FREQUENCY OF INSULIN INJECTIONS

In an attempt to obviate the inconvenience of repeated subcutaneous injections we have experimented with other methods of administration. Thus, insulin has been given by mouth, with and without alkali, and without previous administration of ice water. It was thought that the ice water might inhibit the intestinal secretions and thus prevent the destructive effect of the digestive ferments. Results were negative. The administration of insulin by rectum and through the mucous membrane of the nose have also been attempted without much success. Intravenous injections may be useful in emergencies, as shown by reports from Toronto, but for general practice the subcutaneous injection is apparently the only method of practical value. The site chosen for injection is of minor consideration, although it is well to select parts of the skin which are loose and not subject to friction, tension or pressure; the arm, thigh, side, or buttocks are suitable. If repeated injections are made in one

locality, induration may result, but this is harmless. The first few injections are sometimes painful, causing slight local stinging, and occasionally local heat and swelling. This, however, is transitory and usually, after a few injections, no further difficulty is encountered. Patients, as a rule, accustom themselves easily to these daily injections and object little to the inconvenience. Many of them learn to administer their own hypodermic injections. The technic is simple. Sterile precautions, of course, are necessary.

The dose, as has been stated, depends on the patient's tolerance and the diet; 20 to 30 units are usually sufficient to permit the assimilation of a food allowance of 2500 to 3000 calories, if this is suitably proportioned in fat, carbohydrate, and protein. The time and frequency of injection is still a subject of study. The action of insulin is transitory and is practically spent within twelve hours, although there is evidence suggesting that the effect of a large dose may be prolonged beyond that time. At least one injection a day is necessary. In a number of patients receiving daily doses varying in size proportionately with the severity of the disease, the blood sugar has been estimated at repeated intervals for the entire twenty-four-hour day, both when the entire dose was given in a single morning injection, and when it was divided into two or three distributed smaller injections. The practical advantages of the single injection are obvious, and when the dose can be given effectively at one time, it seems best to give it in the morning before breakfast.

The curves in Figs. 1, 2, 3, and 4 reveal, graphically, typical results of comparative studies of the effect of a single morning injection of a daily quota, and multiple distributed injections of the quota. The diet in all of these cases was divided into three equal meals which were served at 8:10 a.m., 12:10 p.m., and 5:10 p.m. The patients were up and around the wards, but were not allowed to leave the hospital. The insulin had been carefully assayed clinically, and was of tested strength. The same lot of insulin was used throughout each series of observations. Controlled periods of from four to seven days on a

standard régime preceded the day of special study. The results of the foregoing studies have led to tentative conclusions as a basis for practice as follows:

1. In cases that are mild enough to require not more than 15 units of insulin daily (Fig. 1), a single injection of the entire dose administered immediately before breakfast, usually accomplishes a depression of the blood sugar sufficient to avoid glycosuria, except during a short interval in the evening. Apparently the effect of this small dose is spent by suppertime, and the

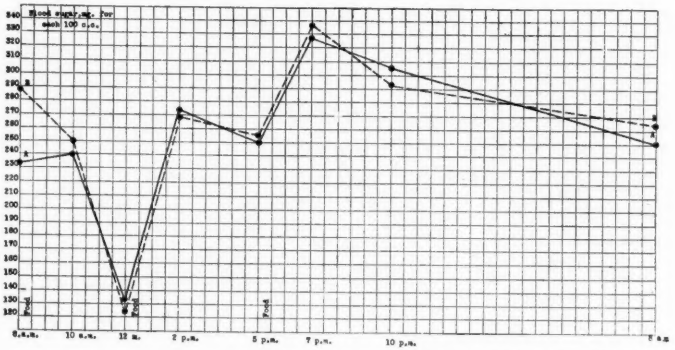


Fig. 1.—Curve A. Case A417972. Diet: Carbohydrate 67, protein 55, fat 227, equally divided in three meals. Insulin (15 units iletin 729,748) given at 8:05 a.m. Evening specimen of urine positive for sugar; morning specimen negative; mixed twenty-four-hour collection, trace. Curve B. Case A417654. Diet: Carbohydrate 57.5, protein 55, fat 227, equally divided in three meals. Insulin (15 units iletin 729,748) given at 8:05 a.m. Evening specimen of urine positive for sugar; morning specimen negative; mixed twenty-four-hour collection, trace.

sugar from this meal causes the blood sugar level to overreach the renal threshold. The following night fast, however, is sufficient again to clear the urine. In such cases, therefore, it does not seem necessary to give more than one injection. The two cases shown in Fig. 1 are somewhat atypical, in that the renal thresholds are unusually high. The amount of sugar excreted by patients of this group does not affect the mixed twenty-four-hour specimen more than enough to show as a faint trace in the qualitative analysis.

2. In cases of moderate severity, requiring 20 to 30 units a day (Fig. 2), a single morning injection causes a rapid depression of the blood sugar level with the low point reached just before the noon meal. The effect is sufficiently prolonged to retard the subsequent elevation of the level until well after supper and, thus to avoid glycosuria except for a few hours in the early morning. In such cases the amount of sugar excreted

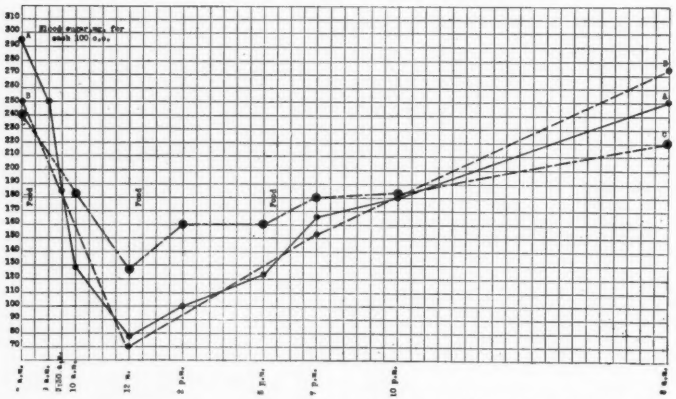


Fig. 2.—Curves A and B. Case A409769. Diet: Carbohydrate 39, protein 48, fat 222, equally divided in three meals. Insulin (30 units iletin B1439) given at 8:05 a.m. Evening specimen of urine negative for sugar; morning specimen positive; mixed twenty-four-hour collection, trace. Curve C. Case A411514. Diet: Carbohydrate 39, protein 39, fat 210, equally divided in three meals. Insulin (30 units iletin 725708) given at 8:05 a.m. Evening specimen of urine negative for sugar; morning specimen trace; mixed twenty-four-hour collection, negative.

is seldom sufficient to appear in the mixed twenty-four-hour specimen as more than a trace.

3. In cases of such severity as to require more than 30 units, satisfactory results are accomplished by two distributed injections, 25 units being given in the morning before breakfast, and the balance of the daily quota at 3:00 p.m. Curve A, Fig. 3, illustrates that when more than 30 units are administered at one time in such a severe case, hypoglycemia and reaction may be provoked some time before the noon meal, despite a high

morning blood sugar, and that the effect of the insulin is not prolonged sufficiently to maintain a sugar-free urine for more than a few hours. Curve B, Fig. 3, was obtained when a total twenty-four-hour dose of 40 units was distributed in divided doses, 15 units at 8:05 a.m., 15 units at 12:05 p.m., and 10 units at 5:00 p.m. In this case a satisfactorily low curve was ob-

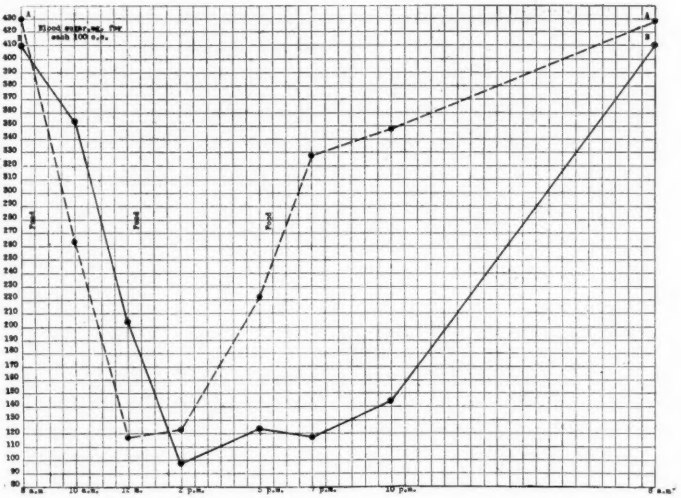


Fig. 3.—Curve A. Case A414460. Diet: Carbohydrate 38, protein 45, fat 200, equally divided in three meals. Insulin (40 units iletin 729,752) given at 8:05 a.m. Evening specimen of urine positive for sugar; morning specimen positive; mixed twenty-four-hour collection positive, 32.7 gm. Curve B. Same case and diet. Insulin (40 units iletin 729,752) given in three doses, 15 units at 8:05 a.m., 15 units at 12:05 p.m., and 10 units at 5:05 p.m. Evening specimen of urine negative for sugar; morning specimen positive; mixed twenty-four-hour collection, positive, 7.95 gm.

tained, but the cumulative effect of the second dose at 12:05 resulted in the low point of the curve being reached at 2:00 p.m., and provoked a reaction. When, however, two doses are given, one before breakfast, and the second dose was given at 3:00 p.m. (Fig. 4), two low points appear, one before dinner and the other before supper, the meals preventing reactions.

A strong argument in favor of a single injection in the milder cases, and the double injection (Fig. 4) in cases requiring more than 30 units daily, is that the low points in the blood sugar level occur at hours when the patient is most likely to be awake and under observation. With doses distributed over the entire twenty-four hours, and particularly, with injections in the evening or at night, as has been advocated for the purpose of holding the blood sugar at a low level during the night, the maximal depression of the blood sugar, it is feared, might occur when the patient is asleep. Under such circumstances the danger of a fatal hypoglycemia would certainly be greater. However, it may be questioned whether it is not theoretically desir-

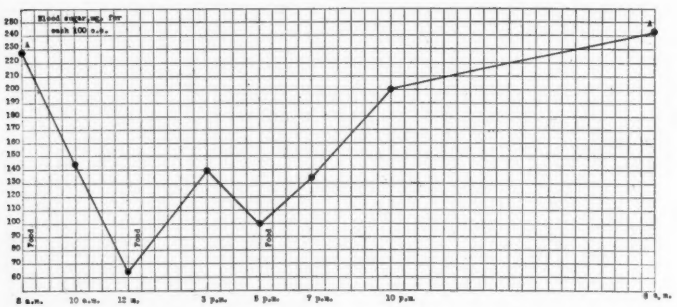


Fig. 4.—Curve A. Case A415702. Diet: Carbohydrate 21, protein 65, fat 176, equally divided in three meals. Insulin (40 units iletin 725753) given in two doses, 25 units at 8:05 a.m. and 15 units at 3 p.m. Evening specimen of urine negative for sugar; morning specimen negative; mixed twenty-four-hour collection, negative.

able to attempt to maintain the blood sugar at levels lower than those obtained by the methods we have adopted. An attempt of this kind does not now seem advisable particularly, as it is still an open question whether the intermittent hyperglycemia that occurs in patients receiving insulin as it is being administered in the Mayo Clinic has the same significance as the perpetual hyperglycemia of inadequately dieted patients not receiving insulin. So far as we have been able to determine, patients whose injections were timed in the manner described, and who,

therefore, have been intermittently hyperglycemic, have improved in health as consistently as have those in whom an effort was made, by means of multiple distributed injections, to hold the blood sugar at more constant low levels.

When the plan of single morning injections is followed, and this holds also for the severer cases in which 25 units are given at 8:00 a.m., and the balance of the daily quota at 3:00 p.m., it is found that single specimens of urine, one collected at night before the patient retires, and the other in the morning when he arises, serve very well as a guide to treatment, thus obviating the necessity for more frequent analyses of single specimens, or for the continuous twenty-four-hour collection of urine. This is of considerable convenience to the patient who is employed in regular work. If the diet is properly balanced, patients who are receiving only small doses of insulin, 10 or 15 units in one dose in the morning, may find sugar in the evening specimen, and none in the morning specimen. Patients with less tolerance, requiring, therefore, larger single injections, or two injections, one at 8:00 a.m., and the other at 3:00 p.m., should not have sugar in the specimen passed at bedtime, but a definite trace in the morning. On the other hand, if, in either case, both the night and morning urines contain sugar, it is evident that either the diet is too high or the insulin dosage inadequate, and one or the other of these must be corrected. Likewise, if both night and morning urines are free from sugar, an adjustment may be necessary and addition of food or reduction of insulin indicated. Usually, the dose of insulin is not altered, but carbohydrate is added or subtracted from the morning meal as the case progresses.

In combination A or combination B (Table 4) no changes are required either in the diet or in the insulin dose. When both the night and morning urines contain sugar, combination

Table 4

	Night urine	Morning urine	Breakfast
Combination A	No sugar	Sugar	No change
Combination B	Sugar	No sugar	No change
Combination C	Sugar	Sugar	Take away 10 gm. carbohydrate
Combination D	No sugar	No sugar	Add 10 gm. carbohydrate

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C, 10 gm. carbohydrate, are subtracted from the breakfast meal. When both night and morning urines are sugar free, combination D, mild reactions will probably occur, and the diet is then raised by adding 10 gm. carbohydrate to the morning meal. If, despite this, both night and morning specimens remain sugar free, and moderate reactions continue, more carbohydrates should be added. Thus, by juggling the carbohydrate portion of the breakfast, the patient may be maintained in balance.

PROCEDURE IN CASES OF DIABETIC COMA

Three variations of routine management of simple cases were described. The treatment of patients with frank and fully developed coma, and those with extreme acidosis and obviously impending coma, require special consideration. The clinical symptoms of impending coma and coma should be well known. Muscular weakness and drowsiness, particularly with pain in the limbs, the back and the stomach, nausea, abnormal and deep respirations, flushed cheeks, dried and parched tongue, and breath smelling strongly of acetone, are the cardinal signs; unconsciousness and the development of the long, labored breathing known as the Kussmaul respiration, follow. The management of this condition has been materially improved by the introduction of insulin. Rules now in use are as follows:

1. Immediate and absolute rest in bed under the constant supervision of special nurses.
2. Artificial warming by the use of blankets and hot-water bottles.
3. Lavage of the stomach with warm 5 per cent solutions of sodium bicarbonate.
4. Lavage of the lower bowel by an enema of warm soapsuds.
5. Catheterization of the urinary bladder.
6. The administration of fluids, and careful measurement and control of liquid intake, such as hot, clear coffee, fat-free bouillon, and hot water; warm physiologic sodium chlorid solution by rectum, as a retention enema. Adults receive one quart of liquid every six hours; children, half this amount.
7. Support of the heart by digitalis; hypodermic injection

of digifolin, 1 c.c. every four hours for several doses, at least three or four. Digifolin has proved to be very effective and, apparently, does not provoke nausea as easily as the oral administration of tincture of digitalis.

8. Administration of insulin, 30 units subcutaneously at once, buffered by administration by mouth of 150 gm. of orange juice. After three hours, another 150 gm. of orange juice are given. This dose of insulin and the orange juice are repeated every six hours until acidosis is under control.

In case the patient is unable to swallow, 15 gm. of pure dextrose is given every three hours in a 5 per cent solution by a retention enema. In extreme emergencies the intravenous injection of insulin and sugar may be resorted to; only glucose of the greatest purity should be employed, dissolved in freshly distilled water, and administered with all the precautions necessary in making intravenous injections.

It is of vital importance to control the effect of insulin by repeated laboratory examinations of the urine and blood. Not infrequently diabetic acidosis is complicated by urinary retention; therefore, unless urination is unimpeded, the bladder is catheterized and completely emptied once every three hours. Every specimen of urine obtained by catheter or by spontaneous voiding is examined at once for sugar and aceto-acetic acid. Insulin is pushed sufficiently to control acidosis, but not enough completely to rid the urine of sugar; otherwise it may happen that the patient is saved from the coma of diabetes, only to be lost in the coma of hypoglycemia. A small amount of sugar in the urine insures against the danger of hypoglycemia. Examinations of the blood for the sugar content and carbon dioxid combining power are made at frequent intervals, and these analyses are of great assistance as a guide to treatment.

Table 5 contains the important data, and illustrates the rapid and favorable response to this management of a patient who entered the hospital in coma. In Fig. 5 the same data are presented in graphs. It will be noted that this patient (Case A409769) was treated without insulin during the first two days, and that during these two days large doses of sodium

bicarbonate were administered. This was done when insulin was first available for the experimental purpose of testing the severity of the patient's acidosis in order to be better able to evaluate the effect of insulin. Alkali seems to be a valuable adjunct in the

Table 5. Insulin effect on acidosis

Date	Time	Food for twenty-four hours, gm.				Blood sugar, per cent	Blood acetone, mg. per cent	Blood fat, gm. per cent	Urine glucose, gm.	Urine diacetic acid	Plasma carbon dioxid, volume per cent
11- 7-22	Admitted, a.m.	C 20	P 0	F 0	0.312				++++	++++	24.8
On admission. Alkali therapy begun and continued until 10:30 p.m. (122 gm. soda bicarb.)											
11- 8-22	5:00 p.m.									+++	28.6
	8:30 a.m.	C 24	P 46	F 160	0.222				112.8	++	32.5
11- 9-22	8:30 a.m.	C 24	P 46	F 160					79.4	+++	
	4:30 p.m.										25.4
	10:00 p.m.						63.1	8.88		++++	18.0
	10:30 p.m.	Iletin #65784-721941, 20 units followed by glucose, 30 gm.									
11-10-22	8:30 a.m.	C 60	P 0	F 0	0.200	38.1	8.88	71.3	Very faint trace		41.5
	8:50 a.m.	Iletin #65784-721941, 20 units followed by glucose, 15 gm.									
	4:00 p.m.				0.183	44.8	6.73		+		31.4
	5:30 p.m.	Iletin #65784-721941, 10 units followed by glucose, 15 gm.									
11-11-22	9:00 a.m.	C 5	P 12	F 12	0.131	33.9	5.33	Faint trace	Trace		34.5
11-12-22	9:00 a.m.	C 5	P 12	F 12				26.8	Trace		
11-13-22	9:00 a.m.	C 5	P 12	F 12	0.222	40.0	4.32	27.3	0		40.2
11-14-22	9:00 a.m.	C 5	P 12	F 12	0.217	27.5	4.10	33.8	0		50.9
11-15-22	9:00 a.m.	C 5	P 12	F 12				23.0	0		
Case A409769. Mr. S.R., aged twenty-four years, height 179 cm., weight 67 kg.											

treatment of diabetic acidosis, provided it is given promptly and in sufficient amounts to raise the carbon dioxid combining power of the plasma to normal in the manner described by Woodyatt and Cary, which was our usual practice before the introduction of insulin. In the case under discussion alkali accomplished restoration

to consciousness, but the acetone increased so fast that it was difficult to give enough alkali to neutralize it. On the second day the patient relapsed again into coma, and in the evening

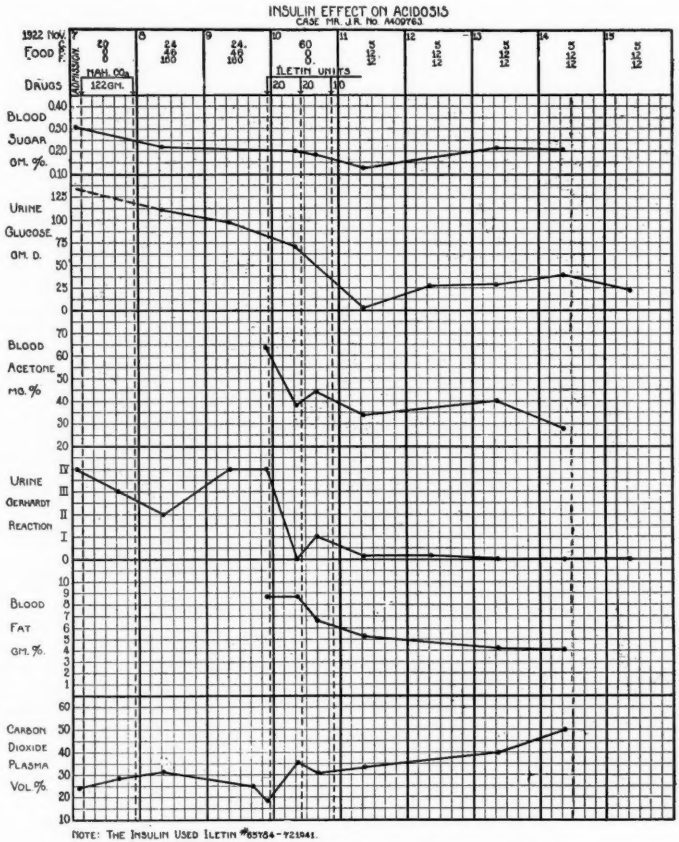

Fig. 5.—Case A409763. Insulin effect on acidosis.

the routine insulin procedure was instituted and the alkali discontinued. While the necessity for alkali appears to be less urgent when insulin is available, and while we have not found it necessary to use it in cases treated with insulin, it may, never-

theless, be inadvisable to dispense with it altogether. An argument against its use is that sodium bicarbonate alters the carbon dioxid combining power of the plasma, thus vitiating this otherwise valuable guide to the degree of acetone production. After the patient has been restored to a safe acid-base equilibrium, his treatment can be continued according to the usual routine (Table 3).

PROCEDURE IN CASES COMPLICATED BY INFECTIONS, INTERCURRENT DISEASES, AND SURGICAL OPERATIONS

It is common knowledge that the severity of diabetes may be at least temporarily increased by infections of all kinds, even by minor maladies, such as acute rhinitis, tonsillitis, and furunculosis. The more severe the infectious process, the more dangerous it becomes in these cases. Heretofore conditions like pneumonia have presented almost insurmountable obstacles. The manipulation of the diet and the insulin dosage in such cases may be extremely difficult, and always demands the constant watchfulness of the medical attendants. The danger lies partly in the rapid fluctuation produced in the patient's tolerance by variations in the degree of intoxication, and partly in the fitfulness of the patient's appetite, and the consequent difficulty of controlling the intake of food. A similarly complex situation is presented in the postoperative condition of patients requiring surgery. Insulin should materially reduce the danger from anesthetics and surgical shock, but only if it is used wisely. In caring for patients with such complications it is our usual practice to limit the diet to liquid foods, such as milk, cream, fruit juices, custard and eggnogs, weighing the amounts of these eaten and calculating the intake of sugar with the customary precision. The carbohydrate content of these diets may be somewhat higher than would otherwise be desirable. Insulin is given in amounts to protect the patient adequately from acidosis, but no special effort is made to control glycosuria until the emergency has passed and the rate of acetone production has subsided. When the critical period is safely over the daily quota of insulin may be reduced and the patient returned to the previous routine. Dur-

ing the periods complicated by severe infections, and, in some postoperative cases, the amount of insulin necessary to control acidosis may be as much as 60, 80, or 100 units a day. It seems that these patients are unusually resistant to the action of insulin. Obviously, it is undesirable to give such large amounts in one injection, and under such circumstances multiple smaller injections are given and the dose is gaged by the result of examination of each specimen of urine as it is passed, giving insulin whenever the specimen shows a positive aceto-acetic acid reaction. Thus, in the case of an adult, if a specimen of urine gives a black aceto-acetic acid reaction, and a strongly positive sugar test, 20 units of insulin may be a proper dose. If the next specimen of urine, collected possibly three hours later, contains sugar, but the Gerhardt test is weaker, a smaller second dose is permitted. If it happens that the next specimen is free from aceto-acetic acid, no further insulin is given, even if this specimen contains a fairly large amount of sugar.

It is important to make certain that urine is not being retained and, especially, in postoperative cases, it is occasionally necessary to catheterize the bladder at regular intervals. It is also of the greatest assistance to examine the blood frequently for its plasma carbon dioxid combining power. Close attention to the clinical condition of the patient is of the utmost importance, and during such crises the physician and nurse must be constantly on the watch for either diabetic coma or overaction of insulin. On the one hand, and always hovering close, is the specter of death from acidosis, and, on the other hand, the danger of hypoglycemia. To pass safely between the two requires judgment and courage. Timidity in the administration of insulin will end the voyage as surely as will reckless and uncontrolled treatment.

It is always wise, when possible, to prepare a patient for operation by a preliminary period of medical treatment, in order to have him in a normal acid base equilibrium at the time of surgical interference. It also seems wise to make sure that the liver is fairly well stored with glycogen. To accomplish this the carbohydrate allowance of the diet may be raised to 100 gm.

daily for a day or two before operation, adequate provision being made for its assimilation by increasing the dose of insulin proportionately. On the morning of the operation food is withheld; nevertheless, an injection of 20 units of insulin is made one-half hour before the time scheduled for the operation. The hyperglycemia provoked by the shock of operation, or by the anesthetic, will serve as a buffer for this injection.

CONCLUSION

It is to be expected that further improvement in the treatment of diabetes will soon be forthcoming. The wide-spread interest in this field which has been stimulated by the introduction of insulin, and the numerous chemical and clinical investigations now in progress in many centers will, undoubtedly, bear fruit in the form of further advances. In the interval, it is the obvious duty of the profession to make the best possible use of insulin which, if used wisely, should as materially improve the life expectancy of the diabetic patient as it certainly adds immeasurably to his feeling of well-being and happiness.

BIBLIOGRAPHY

All articles preceded by an asterisk are of clinical interest.

*1. Allen, F. M.: Studies concerning glycosuria and diabetes. Boston, W. M. Leonard, 1913, 1197 pp.

2. Allen, F. M.: Experimental studies in diabetes. Series II. Changes in assimilation by alteration of body mass. Am. Jour. Med. Sc., 1921, clxi, 16–32.

3. Allen, F. M., and DuBois, E. F.: Clinical calorimetry. Seventeenth paper. Metabolism and treatment in diabetes. Arch. Int. Med., 1916, xvii, 1010–1059.

*4. Allen, F. M., Stillman, E., and Fitz, R.: Total dietary regulation in the treatment of diabetes. New York, Rockefeller Institute Med. Res., 1919, Monograph No. 11.

5. Banting, F. G., and Best, C. H.: The internal secretion of the pancreas. Jour. Lab. and Clin. Med., 1922, vii, 251–266.

6. Banting, F. G., and Best, C. H.: Pancreatic extracts. Jour. Lab. and Clin. Med., 1922, vii, 464–472.

7. Banting, F. G., Best, C. H., Collip, J. B., Campbell, W. F., and Fletcher, A. A.: Pancreatic extracts in the treatment of diabetes mellitus. Canad. Med. Assn. Jour., 1922, xii, 141–146.

8. Banting, F. G., Best, C. H., Collip, J. B., Macleod, J. J. R., and Noble, E. C.: Tr. Roy. Soc. Canad., 1922, xvi, Sect. v.

9. Banting, F. G., Best, C. H., Collip, J. B., Macleod, J. J. R., and Noble, E. C.: The effect of a pancreatic extract (insulin) on normal rabbits. Am. Jour. Physiol., 1922, lxii, 162–176.
10. Banting, F. G., Best, C. H., and Macleod, J. J. R.: The internal secretion of the pancreas. Am. Jour. Physiol., 1922, lix, 479.
11. Boothby, W. M., and Sandiford, Irene. Summary of the basal metabolism data on 8614 subjects with special reference to the normal standards for estimation of the basal metabolic rate. Jour. Biol. Chem., 1922, liv, 783–803.
12. Boothby, W. M., and Sandiford, R. B.: Nomographic charts for the calculation of the metabolic rate by the gasometer method. Boston Med. and Surg. Jour., 1921, clxxxv, 337–354.
13. Brunner, J. C.: Experimenta nova circa pancreas. Accedit diatribe de lympha et genuino pancreatis usu. Amsteloedami, H. Wetstenium, 1683, 168 pp.
*14. Cary, W. E.: Massive doses of alkali in two cases of impending diabetic coma. Jour. Am. Med. Assn., 1921, lxxvi, 1393–1395.
15. Clarke, A. H.: The interrelation of the surviving heart and pancreas of the dog in sugar metabolism. Jour. Exper. Med., 1917, xxvi, 721–744.
16. Clarke, A. H.: The interrelation of the surviving heart and pancreas of the dog in sugar metabolism. Johns Hopkins Hosp. Rep., 1919, xviii, 229–258.
17. Clough, H. D., Stokes, A. M., Gibbs, C. B. F., Stone, N. C., and Murlin, J. R.: Influence of pancreatic perfusates upon the carbohydrate metabolism of depancreatized animals. Proc. Soc. Exper. Biol. and Med., 1922, xx, 66–68.
18. DuBois, D., and DuBois, E. F.: Clinical calorimetry. Tenth paper. A formula to estimate the approximate surface area if height and weight be known. Arch. Int. Med., 1916, xvii, 865–871.
19. Falta, W.: The ductless glandular diseases. Translated and edited by M. K. Meyers. Philadelphia, Blakiston's, 1915, 692 pp.
*20. Joslin, E. P.: Present-day treatment and prognosis in diabetes. Am. Jour. Med. Sc., 1915, cl, 485–496.
*21. Joslin, E. P.: The treatment of diabetes mellitus. 2 ed. Philadelphia, Lea & Febiger, 1917, 559 pp.
*22. Joslin, E. P.: Diabetes mellitus. In: Oxford Medicine. London, Oxford Univ. Press, 1921, iv, 131–177.
23. Kleiner, I. S.: The physiological action of some pyrimidine compounds of the barbituric acid series. Jour. Biol. Chem., 1912, xi, 443–470.
24. Lépine, R.: Nouvelle théorie du diabète. Lyon méd., 1889, lxii, 619–621.
25. Lipka, J.: Graphical and mechanical computations. New York, Wiley & Son, 1918, 264 pp.
26. Lusk, G.: Fundamental ideas regarding basal metabolism. Jour. Am. Med. Assn., 1921, lxxvii, 250–252.
27. Macleod, J. J. R.: Pancreatic extract and diabetes. Canad. Med. Assn. Jour., 1922, xii.
*28. Macleod, J. J. R.: Insulin and diabetes. Brit. Med. Jour., 1922, ii, 833–835.

29. Magnus-Levy, A.: Ueber den Diabetes in Kriege. Deutsch. med. Wchnschr., 1919, xlv, 1379–1382.
30. Mann, F. C., and Magath, T. B.: Studies on the physiology of the liver. III. The effect of administration of glucose in the condition following total extirpation of the liver. Arch. Int. Med., 1922, xxx, 171–181.
31. Marsh, H. E., Newburgh, L. H., and Holly, L. E.: The nitrogen requirement for maintenance in diabetes mellitus. Arch. Int. Med., 1922, xxix, 97–130.
32. Mering, J. V., and Minkowski, O.: Diabetes mellitus nach Pankreasexstirpation. Arch. f. exper. Path. u. Pharmakol., 1890, xxvi, 371–387.
33. Minkowski, O.: Untersuchungen über den Diabetes mellitus nach Exstirpation des Pankreas. Arch. f. exper. Path. u. Pharmakol., 1893, xxxi, 85–189.
34. Minkowski, O.: Diabetes und Balneologie. Deutsch. med. Wchnschr., 1922, xlviii, 475–477.
35. Murlin, J. R.: On the law of surface area in energy metabolism. Science, 1921, liv, 196–200.
36. Murlin, J. R.: Properties and methods of preparation of the antidiabetic substance (glucopyron) generated by the pancreas. Proc. Soc. Exper. Biol. and Med., 1922, xx, 70.
37. Murlin, J. R., and Kramer, B.: The influence of pancreatic and duodenal extracts on the glycosuria and the respiratory metabolism of depancreatized dogs. Jour. Biol. Chem., 1913, xv, 365–383.
*38. Newburgh, L. H., and Marsh, P. L.: The use of a high fat diet in the treatment of diabetes mellitus. Arch. Int. Med., 1920, xxvi, 647–662.
*39. Newburgh, L. H., and Marsh, P. L.: The use of a high fat diet in the treatment of diabetes mellitus. Second paper. Blood sugar. Arch. Int. Med., 1921, xxvii, 699–705.
40. Scott, E. L.: On the influence of intravenous injections of an extract of the pancreas on experimental pancreatic diabetes. Am. Jour. Physiol., 1912, xxix, 306–310.
41. Senn, N.: The surgery of the pancreas, as based upon experiments and clinical researches. Tr. Am. Surg. Assn., 1886, iv, 99–232.
42. Shaffer, P. A.: Antiketogenesis. I. An in vitro analogy. Jour. Biol. Chem., 1921, xlvii, 433–448.
43. Shaffer, P. A.: II. The ketogenic antiketogenic balance in man. Jour. Biol. Chem., 1921, xlvii, 449–473.
44. Shaffer, P. A.: III. Calculation of ketogenic balance from respiratory quotients. Jour. Biol. Chem., 1921, xlix, 143–162.
45. Shaffer, P. A.: IV. The ketogenic-antiketogenic balance in man and its significance in diabetes. Jour. Biol. Chem., 1922, liv, 399–441.
46. Sutter, C. C., and Murlin, J. R.: Three months' study of the influence of the antidiabetic substance on a case of severe diabetes. Proc. Soc. Exper. Biol. and Med., 1922, xx, 68–69.
*47. Wilder, R. M.: Optimal food mixtures for diabetic patients. Jour. Am. Med. Assn., 1922, lxxviii, 1878–1884.
48. Wilder, R. M., Boothby, W. M., and Beeler, Carol: Studies of the metabolism of diabetes. Jour. Biol. Chem., 1922, li, 311–357.

49. Wilder, R. M., and Winter, M. D.: The threshold of ketogenesis. Jour. Biol. Chem., 1922, lii, 393–401.

*50. Woodyatt, R. T.: Acidosis. In: Nelson's Loose Leaf Medicine, New York, 1920, iii, 15–16.

*51. Woodyatt, R. T.: Objects and method of diet adjustment in diabetes. Arch. Int. Med., 1921, xxviii, 125–141.

*52. A special insulin issue of the Journal of Metabolic Research (Volume ii, Numbers 5 and 6), 1922, contains the following papers:

(*a*) Banting, F. G., Campbell, W. R., and Fletcher, A. A.: Insulin in the treatment of diabetes mellitus, 547–604.

(*b*) Campbell, W. R.: Ketosis, acidosis and coma treated by insulin, 605–636.

(*c*) Fletcher, A. A., and Campbell, W. R.: Blood sugar following insulin administration and the symptom complex; hypoglycemia, 637–650.

(*d*) Joslin, E. P., Gray, H., and Root, H. F.: Insulin in hospital and home, 651–700.

(*e*) Wilder, R. M., Boothby, W. M., Barborka, C. J., Kitchen, H. D., and Adams, S. F.: Clinical observations on insulin, 701–728.

(*f*) Williams, J. R.: A clinical study of the effects of insulin in severe diabetes, 729–752.

(*g*) Fitz, R., Murphy, W. P., and Grant, S. B.: Effect of insulin on the metabolism of diabetes, 753–766.

(*h*) Geyelin, H. R., Harrop, G., Murray, M. F., and Corwin, E.: The use of insulin in juvenile diabetes, 767–792.

(*i*) Woodyatt, R. T.: The clinical use of insulin, 793–802.

(*j*) Allen, F. M., and Sherrill, J. W.: Clinical observations with insulin. 1. The use of insulin in diabetic treatment, 803–985.

PRELIMINARY REPORT ON THE EFFECT OF INSULIN ON THE RATE OF HEAT PRODUCTION AND ITS SIGNIFICANCE IN REGARD TO THE CALORIGENIC ACTION OF ADRENALIN

WALTER M. BOOTHBY
AND
RUSSELL M. WILDER

FOUR experiments on the effect of insulin on the rate of heat production of one normal person, and of three diabetic patients under standard postabsorptive basal conditions are reported. In the first experiment (Fig. 6) as a result of administering 20 units of iletin, the blood sugar fell in successive determinations from 286 to 222, 217, and 143, reaching 100 mg. in three hours and twenty minutes, or at a rate which was quite constant, of about 1 mg. each minute. During this time the basal metabolic rate remained essentially constant, the several determinations being −17, −18, −20, −17, and −22 per cent. After the blood sugar fell to 100 mg., the direction of the curve became much less steep, and during the next hour fell only 9 mg.; the basal metabolic rate at this point, however, rose to −10 per cent. The respiratory quotient before the administration of insulin was 0.75, and afterward increased to 0.82, 0.82, 0.85, 0.81, and 0.79. Subsequently 0.5 mg. adrenalin was administered subcutaneously, with an immediate and further rise in the metabolism to −5 per cent, in the respiratory quotient from 0.79 to 0.81, and in the blood sugar from 91 to 111 mg. The other three experiments (Figs. 7, 8, and 9) likewise showed that insulin apparently does not directly increase the rate of heat production, and therefore cannot be considered as a true calorigenic agent.

There is, however, an increase in the metabolism as the blood sugar falls to what, for that individual, is the critical level for

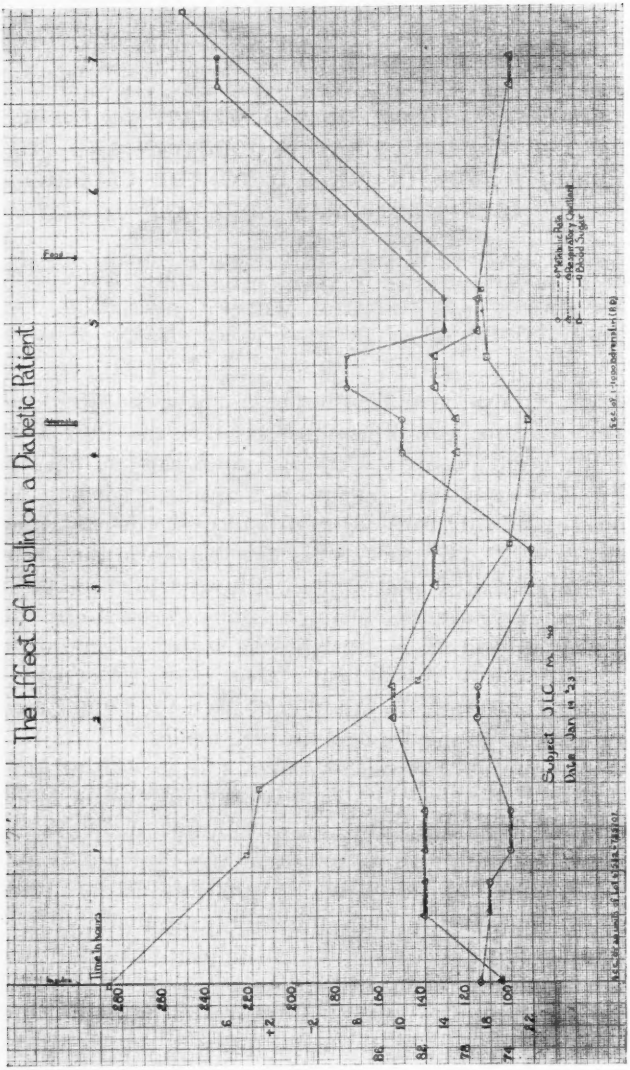
The Effect of Insulin on a Diabetic Patient
Time in hours
Subject J.L.C. No. 349
Date Jan 19 '23
Metabolic Rate
Blood Sugar
Blood Sugar Fasting
Blood Sugar (1.6)

Fig. 6.

the onset of the symptoms of hypoglycemia. The increase in metabolism at this point seems to be secondary to the low level of the blood sugar, or rather to the mechanism that alters the direction of the drop in the blood-sugar curve when the latter reaches its critical level. At this point the shape of the metabolism curve and the other phenomena observed are so similar to that after the administration of adrenalin that the possibility of a spontaneous discharge of epinephrin must be considered.

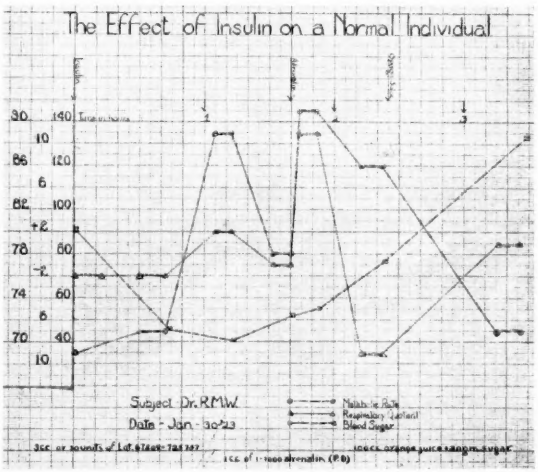

Fig. 7.

In all the experiments in which 0.5 mg. adrenalin was injected subcutaneously between 30 and 255 minutes after the administration of insulin, a definite calorigenic action was produced by the adrenalin, regardless of its influence, or that of insulin on the blood sugar concentration.* If the adrenalin was administered at a point when the blood sugar was approaching the critical level, there was a slight recovery of the blood sugar level amounting to a few milligrams. If the adrenalin was adminis-

* Boothby, W. M., and Sandiford, Irene: The calorigenic action of adrenalin chlorid, Am. Jour. Physiol., 1923. (In press.)

tered while the blood sugar curve was still falling, there might be even an acceleration of the drop in blood sugar, corresponding with the increased metabolism. These experiments are additional evidence to that previously presented by Boothby and Sandiford to the effect that the calorigenic action of adrenalin is not primarily dependent on the concentration of carbohydrate

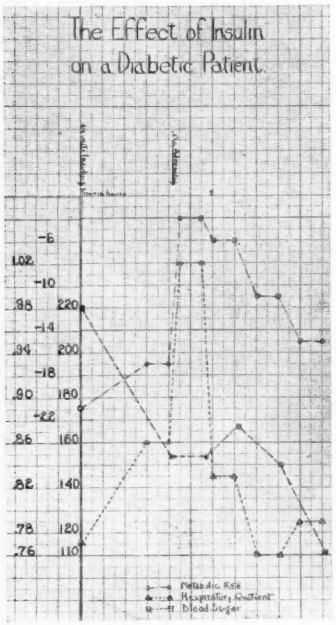

Fig. 8.

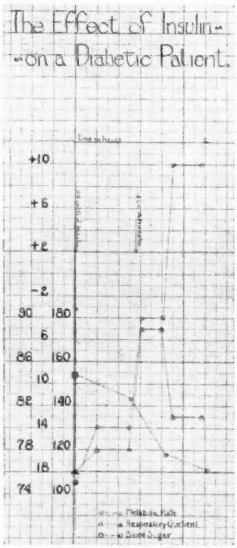

Fig. 9.

metabolites in the blood stream. Besides these acute experiments, many patients have received a daily dose of insulin over long periods without the slightest effect on the level of the basal metabolic rate.

Insulin, therefore, is not a calorigenic agent like thyroxin with a delayed reaction, nor, probably, does it in itself possess an immediate calorigenic action like adrenalin.

STRICTURE OF THE ESOPHAGUS FOLLOWING TYPHOID FEVER

PORTER P. VINSON

ULCERATION in the esophagus is one of the rare manifestations of typhoid fever. In 2000 postmortem examinations reported by Hölscher the condition was found only once. Louis, however, found such lesions in seven of forty-six postmortems, and Mitchell, in the Johns Hopkins Hospital, found them in one of fifty-six. The ulcers, as described by Louis, are most often observed near the cardia and are usually superficial, but may extend to the muscular coat. None of those observed by him had perforated. All of his patients had had the disease at least sixteen days before death. He believed the ulcerations to be secondary processes only. In Mitchell's case typhoid bacilli could not be recovered from the ulcers, although the lesions were similar to cicatrizing typhoid ulcers of the intestine.

In 1904 Thompson reported three cases of his own of stricture of the esophagus following attacks of typhoid fever, and added nine from the literature. Still another case was reported by Turner in 1902. It is quite evident that these strictures followed the healing of ulcers that occurred during the course of the typhoid fever. I have been unable to find in the literature any later reports.

Since 1909 thirteen such cases have been under observation in the Mayo Clinic, and I also know of a similar case elsewhere not yet recorded. Since this condition is so rare, a résumé of the cases may be of interest.

ABSTRACTS OF CASE HISTORIES

Case 1 (A20457). B. F. E., a young man, aged eighteen years, had had typhoid fever in May, 1908, and had been confined to his bed for seven weeks. Before he was able to be up it was noticed that capsules became obstructed

in the lower portion of the esophagus and at the first attempt to swallow solid food he found that it would not pass into the stomach. The degree of dysphagia had varied considerably; at times fluids could be taken fairly easily, while at others closure was complete, and rectal feeding became necessary. He came to the Clinic in February, 1909, with almost complete obstruction of the esophagus. A stricture located just above the cardia was gradually dilated to 40 F. with complete relief from dysphagia.

Case 2 (A23384). A. J., a boy, aged thirteen years, had had typhoid fever for twenty-eight days in December, 1907. He had been confined to bed about six weeks. During convalescence he had been unable to swallow solid food, and liquids had passed into the stomach very slowly. Later the esophagus had become completely obstructed, and February 22, 1908 gastrostomy was performed. After a few days the patient was able to drink a little fluid, but the stricture closed again. When he presented himself at the Clinic for examination in May, 1909 there was no evidence of an opening through the esophagus.

Case 3 (A36814). J. K., a man aged forty-one years, had contracted typhoid fever in September, 1908, and after three weeks of fever, dysphagia had occurred. This had gradually become worse for three weeks, when an "abscess" had apparently ruptured in the throat, discharging blood and pus for several days. Since then there had been increasing dysphagia, but from two to six o'clock in the afternoons deglutition had been comparatively free. A diagnosis of carcinoma of the esophagus had been made. In January, 1909 deglutition was free for a week, after which there was complete obstruction. A gastrostomy was performed February 9, 1909, and the patient gained sixty-six pounds in weight. The patient came to the Clinic April 23, 1910. The stricture was easily dilated to 45 F., and complete relief followed. The gastrostomy was allowed to close, and further dilatations were carried out at home.

Case 4 (A49426). D. D., a man aged thirty-one years, had had typhoid fever in October, 1906, and had been very sick for six weeks; then the temperature became normal for two days, after which there was a relapse lasting five weeks, accompanied by intestinal hemorrhages. After this illness the patient was not able to swallow solid foods, but liquids could be taken quite easily. Examination at the Clinic February 17, 1911 revealed a stricture of the esophagus 25 cm. from the incisor teeth. This was dilated to 40 F., and normal deglutition was restored. Further dilatations were carried out under the direction of the home physician.

Case 5 (A51446). G. L., a boy, aged fifteen years, had had typhoid fever for six weeks, eighteen months before. Following this, dysphagia occurred, but sufficient food had been taken to maintain normal weight. Examination April 6, 1911 revealed an esophageal stricture 31 cm. from the incisor teeth, which was dilated to 38 F. Further dilatations were continued at home.

Case 6 (A264959). E. S., a man aged twenty-three years, had had an attack of typhoid fever in 1909; eight weeks afterward it was noted that solid food seemed to stick in the esophagus in the middle sternal region. One month later fluids only could be swallowed, and after two months the stricture closed completely. A gastrostomy was performed. Ten years later

the patient came to the Clinic. An impermeable stricture 21 cm. from the incisor teeth was found.

Case 7 (A303074). O. K., a man aged forty-seven years, had had typhoid fever in 1913, and during convalescence had had difficulty in swallowing pills. A stomach-tube was passed occasionally, with consequent improvement, and very little trouble was experienced until three days before coming to the Clinic in January, 1920. A short stricture, 27 cm. from the incisor teeth, was found, and was dilated to 47 F., with complete relief from symptoms.

Case 8 (A323606). P. H. M., a man aged twenty-six years, had had dysphagia immediately after an attack of typhoid fever in July, 1906. The dysphagia progressed gradually for about six months when gastrostomy became necessary. After the operation the stricture was dilated once or twice, and then allowed to close completely. Examination at the Clinic July 8, 1920 revealed an impermeable stricture.

Case 9 (A329385). F. K., a woman aged twenty-seven years, had had dysphagia following a severe attack of typhoid fever in 1916. Since the onset of her trouble she had lived entirely on liquids taken from a treaspoon. Examination at the Clinic Aguust 13, 1920 revealed a short stricture, 37 cm. from the incisor teeth; this was dilated to 47 F. with complete relief from dysphagia.

Case 10 (A386153). D. T., a youth aged eighteen years, had had dysphagia eighteen months before, during convalescence from an attack of typhoid fever. In April, 1921 gastrostomy had been performed. He came to the Clinic in March, 1922, but he had been told that his stricture was impassable, and he would not consent to an esophagoscopic examination.

Case 11 (A61770). W. R., a boy, aged sixteen years, had had typhoid fever two years before coming to the Clinic, in December, 1911. Five weeks after the onset of the disease difficulty in swallowing had been noticed. This condition had become progressively worse with periods of complete closure of two or three days' duration; for four days there had been complete obstruction. A short stricture, 17.5 cm. from the incisor teeth, was dilated to 45 F. with complete relief from dysphagia. Dilatations were continued at home. In December, 1920 the patient returned for further observation, at which time he had slight dysphagia. The stricture was again dilated to 45 F. and he was instructed to continue dilatations under the direction of his physician at home.

Case 12 (A125654). H. H., a young woman, aged twenty years, had had typhoid fever in 1906. Slight dysphagia was noticed before she was able to be out of bed, and as soon as she was allowed to take solid food complete closure occurred. This was relieved for a day by the passage of a stomach-tube, but a few days later it was necessary to perform a gastrostomy. When the patient came to the Clinic in March, 1915 a stricture 7.5 cm. above the cardia was dilated to 48 F. April 28, 1916 the gastrostomy wound was closed and the patient was allowed to return home. Further dilatations were carried out there under the direction of a physician.

Case 13 (A199586). J. B., a young woman, had had typhoid fever seven years before coming for examination in June, 1917. Dysphagia was noticed

during a rather prolonged convalescence. She first noticed obstruction to solid food in the upper portion of the esophagus, and later difficulty in swallowing liquids. The symptoms became progressively worse and at the end of a year obstruction was complete. A gastrostomy was performed and an impassable stricture was located 20 cm. from the incisor teeth.

It is notable that in the twenty-six collected cases only three of the patients were women. However, the case reported by Mitchell was in a woman. The stricture was usually located in the lower portion of the esophagus and corresponded with the most common site of ulceration. Of the thirteen patients whose histories had been reported, in the literature, three had died from lack of treatment, one had died during the course of treatment, and three had had gastrostomies, no attempt having been made to keep the strictures patent by dilatations. The remaining six patients were apparently cured by the passage of sounds.

Seven of the thirteen patients seen in the Clinic had had gastrostomies elsewhere, and in four of these the stricture was impermeable. One did not have an esophagoscopic examination, but it is probable that closure was complete. In six of the cases without and in two with gastrostomy normal deglutition was restored by dilating with graduated sounds. It is unfortunate that the five patients with impermeable strictures could not have been treated at a time when dilatations could have been made. In Case 3 it is possible that a rupture of a periesophageal abscess into the esophagus was a part of the pathologic condition. Although purely speculative, it is nevertheless possible that there was a subacute perforation of one of the ulcers, with the formation of an abscess, which later ruptured into the esophagus.

BIBLIOGRAPHY

1. Dugan: Quoted by J. E. Thompson.
2. Hölscher, A.: Ueber die Complicationen bei 2000 Fallen von letalem abdominal-typhus. München. med. Wchnschr., 1891, xxxviii, 43, 62.
3. Louis: Quoted by Thompson.
4. Mitchell, J. F.: On the esophageal complications of typhoid fever. Johns Hopkins Hosp. Rec., 1899–1900, 295–307.
5. Packard, F. A.: Quoted by Thompson.

6. Pyle, J. S.: Stricture of the esophagus resulting from typhoid ulceration, with report of a case introducing a new method of treating esophageal strictures. Philadelphia Med. Jour., 1900, v, 303–304.
7. Roberts: Quoted by Thompson.
8. Summers, J. E.: Quoted by Thompson.
9. Thompson, J. E.: Stricture of the esophagus due to typhoid ulceration. Ann. Surg., 1904, xxxix, 683–689.
10. Tinker, M. B.: Quoted by Thompson.
11. Turner, M. L.: Stricture of the esophagus following typhoid fever. Jour. Iowa State Med. Soc., viii, 586–589.

KYMOGRAPHIC STUDIES OF VARIOUS PATHOLOGIC CONDITIONS OF THE STOMACH

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AND
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KYMOGRAPHIC studies of various pathologic conditions of the stomach were undertaken in an attempt to classify the changes in gastric contractility and intragastric tension under normal and pathologic conditions. It was thought that additional information of value to the clinician in elucidating the problems connected with the pathologic conditions of the stomach could be obtained by a consideration of the results of such studies. The skiagraph, even in the most expert hands, has strict limitations.

REVIEW OF PREVIOUS INVESTIGATIONS

During the last forty years much has been written on the mechanics of gastric digestion, most observers in this field confining themselves to the physiologic aspects of the question. Morat, in 1882, obtained graphic records of gastric motility by means of a large rubber balloon inflated with air. In 1886 Hofmeister and Schutz studied the excised and bloodless stomach of a dog in a moist chamber and found that a contraction wave, appearing a few centimeters from the cardia, moves peristaltically to a point 2 cm. from the antrum. By the manometric method, von Pfungen, in 1887, observed that on the average there were three contractions of the antrum in a minute, each lasting six to twelve seconds. In 1911 Cannon found, as the result of experiments, that when smooth muscle is toneless and flaccid, extension calls forth no response; only when a muscle is shortened and in a state of tonus does pull result in contraction.

Gastric peristalsis results from tension produced by internal pressure acting on tonically shortened gastric musculature. Tonus, as an essential factor of gastric peristalsis, is first given by vagus impulses and is maintained by the stomach itself, for two reasons; first, to sever the vagi before feeding results in inactivity, and, second, to sever the vagi after digestion is started, causing no change in gastric movement or in the rate of discharge. Probably a psychic tonus is developed by the taking of food. The phenomenon of hunger has received considerable attention. The work of Cannon showed that the empty stomach has stronger contractions than the full one, and that these contractions may be irregular and of sudden onset, usually occurring every ninety seconds and lasting thirty seconds. These contraction waves were found to be synchronus with the subject's expression of hunger. Moreover, before hunger was experienced, the recording apparatus revealed no signs of gastric activity.

In 1912 Carlson studied the character of the movement of an empty stomach. His opinion was that contractions of the stomach caused sensations of hunger by stimulating the afferent nerve fibers in the muscle layers, and that these contractions were inhibited by stimulating the gustatory nerve endings. In 1913 he found that hunger contractions in dogs whose stomachs had been isolated from the central nervous system by a section of vagus and sympathetic nerves were the same as the hunger contractions in normal dogs. It therefore follows that the cause of hunger is not due to augmentation of vagus tone.

Rogers is of the opinion that in a rabbit, at least, the gastric hunger contractions are intensified digestive peristalsis. The empty stomach of the rabbit shows very strong, rapidly repeated contractions and marked tonus variations. Excitement inhibits the stomach's contractions and causes a lowering of the tonus of the musculature.

Rogers and Hardt have shown that in man and in dog the fundic end of the stomach exhibits a slow tonus rhythm of one to three minutes' duration during normal digestion. During the emptying of the stomach and the onset of the hunger period

this tonus rhythm becomes more vigorous, and after several hours of starvation, vigorous peristaltic contractions are superimposed on the slow tonus rhythm. They begin at the cardiac end of the stomach and sweep over the whole organ.

The question of the precise nature of the characteristic pain of gastric ulcer has given rise to much argument during late years. Ginsburg, Tympowsky, and Hamburger in reviewing the question assert that, since a concentration of hydrochloric acid exceeding that found even in normal gastric content may be put into the stomach of patients with peptic ulcer without causing pain; acidity alone cannot be the cause of the pain. In furtherance of this theory numerous experiments were performed by them, and as a result they found: (1) that the strong contractions of the stomach accompanying the pain of gastric ulcer seem to confirm the idea that pain is due to tension, (2) that marked hunger contractions cause pain in the hyperirritable condition of the stomach by increasing intragastric pressure, and (3) that hyperacidity alone may be a factor by reflexly causing hypertonus, hyperperistalsis, and pylorospasm, allowing greater tension to be produced.

Hardt, working along the same lines, corroborates these findings. His experiments seem to substantiate the hypothesis that the pain is mainly due to the contraction or spasm of the upper end of the duodenum and the pylorus, together with the peristalsis of the fundus, the acid playing only a secondary part.

In 1919 Homans, using the same method of study as the last named writers, found himself unable to agree with their conclusions. The results in his series seemed to show that pain in patients suffering from proved gastric and duodenal ulcers was not of necessity associated with any recognizable activity of the gastric walls, and that intense gastric activity could occur in these same patients without giving rise to pain. Moreover, in taking many histories in ulcer cases he observed that while accessions of pain were sometimes found to have a rhythmic character, often he observed that the story of pain was continuous and that no interruption or rhythmicity could be read into it.

This brief summary of the results obtained by means of the balloon and kymograph serves to show that apart from the investigation of the origin of pain, this method has hitherto been restricted to the study of gastric motility from a physiologic standpoint only. The pathologic study of gastric movement seems to have been left almost entirely in the hands of the fluoroscopist.

As an example of their work, we quote from Reynolds and McClure, who recently made an interesting communication which embodied the principal results of fluoroscopic observation of stomachs of normal men, and of patients with ulcer of the stomach and duodenum. Patients with ulcer were studied in order to obtain detailed information regarding gastric motor phenomena occurring throughout the period in which the stomach was emptying itself, and during the occurrence of pain due to the presence of the ulcer. The authors concluded: "Peristaltic waves begin high up in the gastric wall at uniform intervals of about twenty seconds and, gradually deepening, progress in an orderly manner to the region of the pyloric sphincter. As each wave approaches the sphincter, the latter opens, allowing chyme to be ejected into the duodenum over a period of about ten seconds.

"Abnormal phenomena observed in the stomachs of patients with gastric or duodenal ulcer were modifications of the motor activities of the stomachs of healthy persons. The abnormalities noted were: (1) exaggerated type of normal gastric peristalsis, (2) irregularity in time of occurrence, depth and length of course of peristaltic waves, (3) partial or complete intermittent spasm of the pyloric sphincter, (4) localized permanent stationary spasm of gastric musculature causing the so-called incisura, (5) gastric antiperistalsis, (6) delayed emptying time of the stomach, and (7) very rapid emptying of the stomach. The onset of pain was accompanied by modifications in whatever type of motor activities the stomach had previously manifested, with two exceptions. The various abnormal motor phenomena were observed in the stomachs of peptic ulcer patients who did not develop pain during the period of observation."

The fluoroscope is therefore capable of showing irregularities in motility occurring in certain types of gastric complaint. Unfortunately, it does not make a sufficiently exact or a sufficiently prolonged record to permit the observer to compare fine alterations in movement. These difficulties are overcome by the kymograph because it gives a record which is both delicate and permanent. Before the kymographic tracing of one person may be compared with the kymographic tracing of another with any degree of accuracy it will be necessary to use some system whereby all experiments may be conducted under the same conditions, and with the same preliminary intragastric tension. The reason for this is obvious if it is recognized that the stomach is an organ varying from time to time, both in cubic capacity and in internal pressure, and that if a balloon is inserted into a stomach which is in a condition of muscular relaxation, more air will be blown into it than if at the moment of insertion the organ were to be strongly contracted. Since we have no means of estimating the physical condition of the stomach at any given time, it is manifestly inaccurate to compare one kymographic tracing with another. To overcome this objection, a method was devised which we believe to be sufficiently exact to enable the observer to compare the intragastric tension of one person with the intragastric tension of another.

METHOD OF PROCEDURE

A thin rubber balloon is tied securely to the rubber coil of a Rehfuss tube inside the balloon, and fixed to the rubber coil is inserted about 12 cm. of a No. 10 English catheter. This gives the balloon enough resistance to enable the patient to take it with a fair amount of comfort (Fig. 10).

The balloon is evacuated, swallowed by the patient, and connected with a calibrated chloroform manometer, in one limb of which there is a float attached to a recording stylo (Fig. 11). By means of a three-way stopcock and an attached syringe sufficient air is pumped into the manometer to raise the chloroform to a definite level. At this stage, by utilization of a stopcock, air is prevented from escaping from the manometer into

the balloon. The next step is to open the connection so that the levels of chloroform in the manometer may readjust themselves, and thus drive a small, but definite amount of air into the balloon. This process is repeated three times, so that at the beginning of the experiment the pressure is uniformly 66 gm. for each square centimeter. Thus the manometer reading gives a ratio, which, if not absolute, at least records relative variations in intragastric tension.

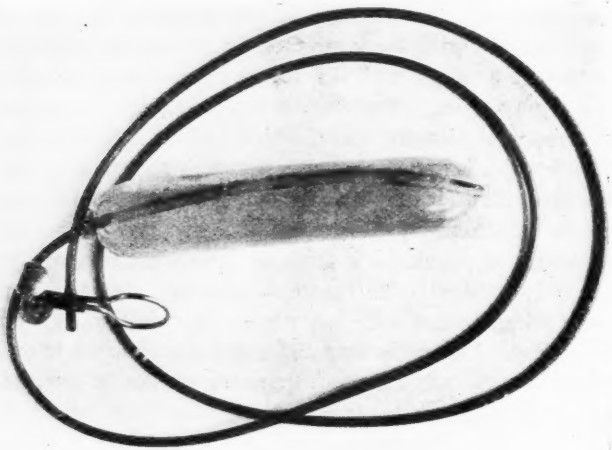

Fig. 10.—Balloon attached to rubber coil of Rehfuss tube.

In order to stabilize the experiment still further, it is conducted at a definite interval after a standardized meal. The meal consists of two poached eggs, the juice of one-half of a grapefruit, two pieces of toast and a glass of boiled milk. The balloon is not passed until five or six hours have elasped, for at this stage the various motor activities of the stomach are accentuated, and are therefore contrasted more readily. From ten to fifteen minutes are usually allowed to elapse after the swallowing of the balloon before the tracing is taken, for it has been found that in a great many instances the action of the

stomach is inhibited by the passage of the balloon for a considerable subsequent period. By the use of this instrument and

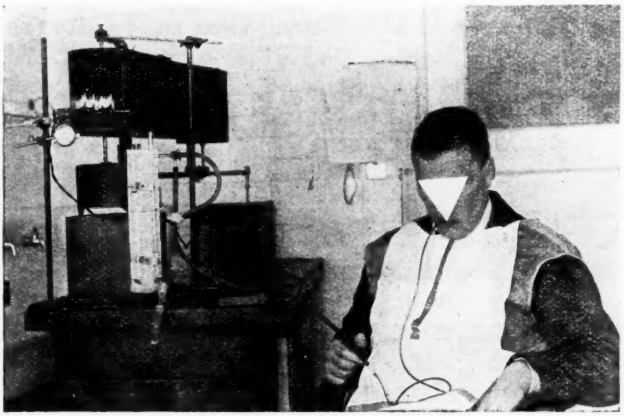

Fig. 11.—Apparatus in position showing manometer, recording stylo, three-way stop-cock, and syringe.

procedure we have investigated and compared the changes in tonus and the variations in tension in 120 patients.

A NORMAL KYMOGRAPHIC TRACING

In 1915 Rogers and Hardt published a paper in which they showed that two main types of movement occurred in normal peristalsis. The first type is a somewhat long, moderately shallow wave which they call "tonus rhythm"; the second type is usually superimposed on the first and is of greater intensity, although of shorter duration. This is called a "peristaltic wave." It should be pointed out that in our kymograms the distance between tracing and base line gives no indication of the intragastric tension; that is measured by means of the calibrated manometer and registered below the base line in figures which may be used to give the pressure in grams for each square centimeter.

CLASSIFICATION OF KYMOGRAMS IN SERIES STUDIED

For the most part the study has been confined to normal persons, to persons with reflex symptoms and negative roentgenograms, and to persons with duodenal ulcers and positive roentgenograms. The kymographic tracings fall into three groups:

In Group 1 the peristaltic waves are diminished, although tonus rhythm may not be greatly altered. On an average the highest intragastric tension is 4.8 gm. for each square centimeter. The free gastric acidity varied too greatly to be of any diagnostic importance. Of twenty-five tracings in this group, seventeen are found to belong to those patients who have duodenal ulcer with positive roentgenograms (Fig. 12).

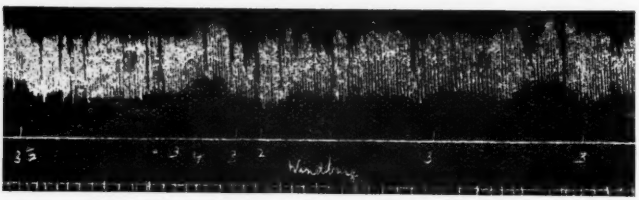

Fig. 12.—A kymograph tracing in Group 1; marked diminution of both peristaltic wave and tonus rhythm.

In Group 2 the peristaltic waves are more active and the tonus rhythm is somewhat accentuated. The highest intragastric tension measures 5.6 gm. for each square centimeter. The amount of free acid seems to have no significance. Of forty tracings in this group, thirty-two are of patients who are either normal or have reflex gastric symptoms and negative roentgenograms (Fig. 13).

In Group 3 the peristaltic waves are greatly increased and the tonus rhythm may or may not be correspondingly increased. The highest intragastric tension in this group measures 11 gm. for each square centimeter, and again the amount of free acid seems to be of no special importance. Of a total of eighty-six cases in our series (Groups 1, 2 and 3), only twenty are in Group 3, and among these the two types are represented, that is, the

duodenal ulcers with positive roentgenograms, and reflex symptoms with negative roentgenograms. Evidently the tracing in the case of ulcer is much the same as in case of functional

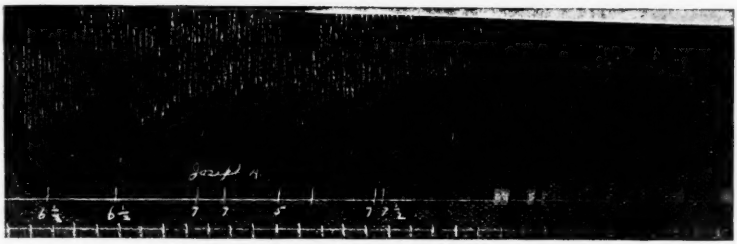

Fig. 13.—A kymograph tracing in Group 2; fairly active peristaltic waves superimposed upon accentuated tonus rhythm.

disorder. No difference can be found between them, either from the point of view of peristaltic waves and tonus rhythm or of intragastric tension. However, in most cases of duodenal ulcer there is a free acidity of over 50, whereas in the bulk of

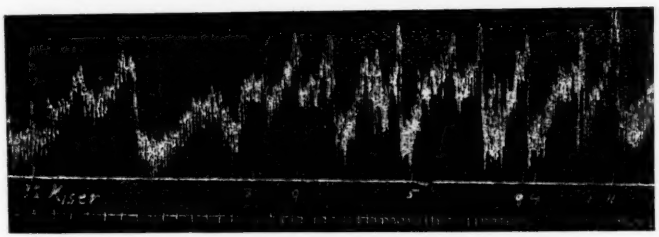

Fig. 14.—A kymograph tracing in Group 3; peristaltic waves and tonus rhythm greatly increased.

functional cases the acidity seems to be below 50. These facts are apparently true in twelve of the twenty cases in Group 3 (Fig. 14).

DIFFICULTIES IN INTERPRETATION

From the illustrations in the foregoing groups it would appear that the classification of kymograph tracing is a fairly obvious

procedure. As a matter of fact the differentiation between Group 1 and Group 2 is by no means clearly demarcated. Certain types of kymograms of duodenal ulcers border on those in Group 2, and again, certain types of those of the functional gastric disorder border on Group 1. It is very difficult to determine where one begins and the other ends, as in all natural phenomena shades of difference are very finely drawn. In the majority of cases it has been shown that if the maximal peristaltic wave in any particular kymogram does not exceed 2 mm. the tracing may be classified as in Group 1, and is usually found to belong to a patient having duodenal ulcer. On the other hand, if the maximal peristaltic wave exceeds 2 mm., the tracing may be classified as belonging to Group 2, and is usually found

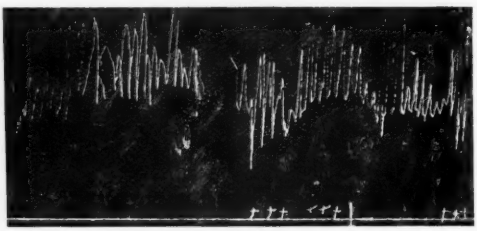

Fig. 15.—A kymograph showing "female type" of respiration.

to be that of a patient with a functional gastric complaint. This is merely an arbitrary standardization which we have used extensively on all the kymograms with the results quoted.

Another factor which adds to the difficulties of interpretation is a difference in reaction of the stomach to respiratory movement. Normally, intragastric tension is increased by inspiration and decreased by expiration; in a few cases the reverse occurs; that is to say, with inspiration, intragastric tension is lowered, and with expiration it is raised. Since this phenomenon is noticed for the most part in women, we have designated it as a "female type of respiration" (Fig. 15).

A still further complication is a combination of both conditions with irregular alternations from the normal to the female type

of respiration. If the observer fails to recognize the type of respiration he is dealing with, he must of necessity get a completely erroneous impression of the kymogram, for what he judges to be changes in gastric tone will in reality be changes in depth of inspiration. In this connection it is of interest to note the reaction of the respiration on the motility of a stomach which was prolapsed into the thorax through a diaphragmatic hernia. The female type of respiration predominated entirely.

Although this so-called female type of respiration is found for the most part in kymograms taken of women, it is sometimes found on kymograms taken of men. It must be understood that the only accurate way of recognizing this condition is actually to watch the kymograph in operation.

STUDIES IN LOW GASTRIC TENSION

As we have said, on an average the highest intragastric tension in Group 1 is 4.8 in grams for each square centimeter. In Group 2 it measures 5.6 gm. for each square centimeter and in Group 3 11 gm. for each square centimeter. These figures from the clinical and kymographic standpoint have given us our normal intragastric tensions for the three groups. Three examples of diminished intragastric tension were studied.

The first example is that of a patient who had been using large doses of veronal and chloral for five months prior to examination in an effort to overcome an excessive nervousness associated with marked insomina; incidentally, the patient was a confirmed alcoholic. The tracing shows diminished peristaltic waves, and but feebly active tonus rhythm. This would undoubtedly be classed with tracings in cases of duodenal ulcer in Group 1, but for the fact that intragastric tension as registered by the manometer is markedly below normal; at certain periods of tracing it was so low as actually to register negative tension. This is in direct contrast to the tracings in cases of duodenal ulcer which showed normal or increased tension.

The second example is the tracing of a patient who complained of complete loss of appetite and general debility. Both tonus rhythm peristaltic waves are very active in the tracing,

but the intragastric tension was markedly lower than the average intragastric tension in Group 2. A decided gain in intragastric tension was observed as a result of daily gastric lavage with cold water and suitable tonics. At the time it was taken the patient had quite recovered his appetite.

The third example is a tracing which would ordinarily be classed in Group 1, that is, in the duodenal ulcer group, but here again intragastric tension was so low as to give rise to the suspicion that the apparatus was leaking, which, however, was not found to be the case. The patient, a young girl, appeared to be very weak and debilitated. She had no interest in life and complained of indefinite abdominal pains with frequent vomiting. Her systolic blood-pressure was 100; the diastolic could not be ascertained. A diagnosis was made of mild dementia præcox and chronic appendicitis; the latter was verified at operation. Clinically one would expect a low intragastric pressure in such a case.

THE EFFECT OF ALKALIS AND BELLADONNA ON INTRAGASTRIC TENSION AND MOTILITY

A series of studies were also carried out in an effort to show the effects on intragastric tension and motility of (1) the alkaline medical régime for duodenal ulcer, and (2) treatment with belladonna. Twenty cases were examined.

Both types of treatment showed much the same results. Peristaltic waves were very markedly diminished. The tonus rhythm in most tracings was greatly modified. On the other hand, intragastric tension remained within normal proportions (Figs. 16 and 17).

The findings, especially those recorded during the alkaline treatment for peptic ulcer of frequent small feedings, would appear to bear out Cannon's work in which he showed that the stomach is strongly contracted in hunger, and that the repeated swallowing of food causes temporary inhibition of gastric tonus.

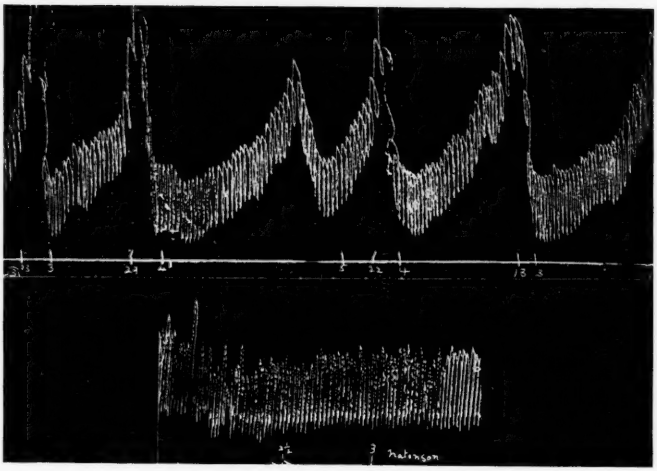

Fig. 16.—*Upper plate:* Before the alkaline medical régime for duodenal ulcer is started the kymograph is in Group 3. *Lower plate:* Result of two weeks' treatment. The kymograph is in Group 1.

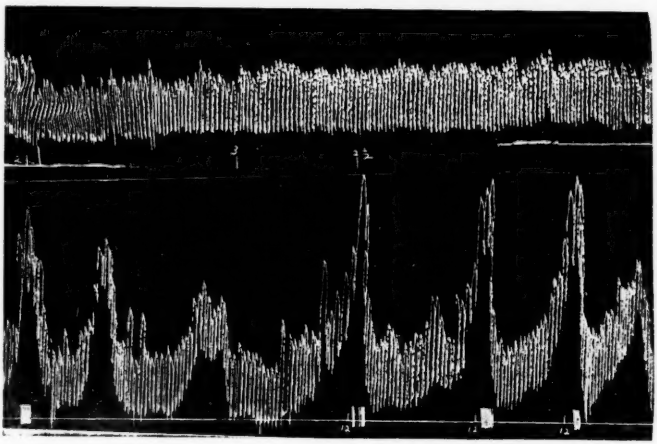

Fig. 17.—*Upper plate:* Result of giving same patient 15 minims of tincture of belladonna. The kymograph is in Group 1 and pain is absent. Two and a half hours later peristalsis became again very vigorous, but pain was still absent. *Lower plate:* Kymograph in Group 3. The high peristaltic waves are associated with pain which is indicated on the base line.

STUDIES IN ETIOLOGY OF GASTRIC PAIN

The factors concerned in the etiology of gastric pain were considered only incidentally in this study. The results further emphasized the view that peristalsis and increased intragastric tension are of primary importance in the etiology of pain. The kymographic study of so large a group of cases offered us an opportunity to bring to light other possible factors which may be essential in the production of pain and which heretofore were not revealed during the studies on a more limited group of cases.

Of the seventeen duodenal ulcer cases in Group 1 in which there were only slight peristaltic waves, only one patient experienced definite ulcer pains. The gastric free acidity varied from 20 to 76, with an average of 43 free acidity in terms of one-tenth normal sodium hydroxid. According to the advocates of the acidity theory as the probable cause of pain, most of the patients in this group should have experienced pain since the acidity was present in sufficient concentration. On the other hand, this one instance in which pain was experienced in the absence of vigorous peristalsis apparently does not support the view that peristalsis is the primary factor in causation of pain.

In Groups 1 and 2 there were twenty-six patients who complained of epigastric distress of a reflex nature which was secondary to various conditions such as appendicitis, chronic constipation, migrain, mild nicotine poisoning, and nervous exhaustion. None of the twenty-six experienced pain. Therefore, out of forty-three patients with epigastric distress, due to extrinsic causes, only one experienced pain during the period in which no vigorous peristalsis was recorded and in all of which there was an adequate acidity.

Of fifteen patients in Group 3 with active peristalsis and increased intragastric pressure, six had duodenal ulcers and nine had epigastric distress of a functional or reflex nature which simulated pain from the ulcer. Of the six patients with ulcer, four had pain synchronous with, or at the end of, an active peristalsis. Two had active peristalsis in the absence of pain. The free acidity in these two cases was 60 and 68 respectively. In patients who had pain simulating peptic ulcer, but in whom

clinically and roentgenologically we were unable to demonstrate an ulcer, active and painful peristalsis occurred. In every instance tincture of belladonna inhibited the peristalsis (Fig. 17) and with the inhibition there was cessation of pain. In one patient the peristalsis was inhibited for two hours, and when it returned there was no pain. The intragastric pressure was higher than before the administrations of belladonna and the peristalsis was equally active. The gastric analysis revealed a free acidity of 60. We are then led to believe that there may be something else besides peristalsis and an adequate acidity necessary to the production of pain, although as yet it has not been definitely demonstrated. We refer to the possibility of a third factor. Apparently the tincture of belladonna may inhibit this third factor more completely than it does the peristalsis or the acidity. This readily explains many of the apparent contradictory results.

Heretofore, we were more inclined to regard the active peristalsis, pylorospasms, and duodenal spasms as being in a sense synonymous with gastric pain. We have not previously considered the possibility that afferent sensory mechanism might be more or less independent of the motor mechanism. One can readily conceive, therefore, that vigorous active peristalsis might be present without stimulating the afferent sensory impulses to any marked degree. The part of the peristalsis in the production of pain would be that of mechanically irritating an already hyperirritable sensory mechanism. We are contemplating a more detailed study of this particular phase of the problem in the near future.

SUMMARY

A method is described whereby changes in gastric motility and intragastric tension may be compared and classified.

An attempt is made to utilize the balloon and kymograph as instruments for diagnosis in determination of pathologic conditions in the stomach.

One hundred twenty kymograms have been taken, and the tracings fell into three characteristic groups:

Group 1. Peristaltic waves are diminished, as also is tonus rhythm. A very large percentage of patients whose kymograms fall into this group have duodenal ulcers with positive roentgenograms.

Group 2. Peristaltic waves are more active and tonus rhythm is accentuated. In striking contrast with Group 1 is the fact that in Group 2 the greater number of subjects are either normal or have reflex gastric symptoms.

Group 3. Peristaltic waves are greatly increased. Tonus rhythm may or may not be correspondingly intensified. This is a very small group, too small from which to draw very definite conclusions.

The few kymograms which have shown diminished intragastric tension are found to belong to those patients who have been suffering from marked general debility and asthenia.

The effect of the alkaline treatment for duodenal ulcer on gastric motility causes marked diminution of the various motor activities of the stomach, although intragastric tension remains within normal proportions.

The action of belladonna produces effects similar to alkaline treatment.

The factors concerned in the etiology of gastric pain are considered. The results emphasize the view that peristalsis and increased intragastric tension are of primary importance in the causation of pain. The experiments with belladonna lead us to believe that there may be something besides peristalsis and an adequate acidity necessary to the production of pain. It is suggested that the afferent sensory mechanism may be inhibited independently of the peristalsis and tonus variation.

BIBLIOGRAPHY

1. Cannon, W. B.: The nature of gastric peristalsis. Am. Jour. Physiol., 1911–1912, xxix, 250–266.
2. Cannon, W. B., and Lieb, C. W.: The receptive relaxation of the stomach. Am. Jour. Physiol., 1911–1912, xxix, 267–273.
3. Carlson, A. J.: Contributions to the physiology of the stomach. II. The relation between the contractions of the empty stomach and the sensation of hunger. Am. Jour. Physiol., 1912–1913, xxxi, 175–192.

4. Carlson, A. J.: Contributions to the physiology of the stomach. VI. A study of the mechanisms of the hunger contractions of the empty stomach by experiments on dogs. Am. Jour. Physiol., 1913, xxxii, 369–388.
5. Ginsburg, H., Tumpowsky, I., and Hamburger, W. W.: The newer interpretation of the gastric pain in chronic ulcer. Jour. Am. Med. Assn., 1916, lxvii, 990–994.
6. Hardt, L. L. J.: Pain in active pathologic processes in stomach or duodenum. Jour. Am. Med. Assn., 1918, lxx, 837–839.
7. Hardt, L. L. J.: Studies of the cause of pain in gastric and duodenal ulcers; peristalsis as direct cause of pain in gastric ulcers with achylia and in duodenal ulcers. Arch. Int. Med., 1922, xxix, 684–689.
8. Hofmeister, F., and Schütz: Quoted by Cannon, W. B.: The movements of stomach studied by means of the röntgen rays. Am. Jour. Physiol., 1898, i, 359–382.
9. Homans, J.: The relation of pain in gastric and duodenal ulcer to muscular activity of the stomach. Am. Jour. Med. Sc., 1919, clvii, 74–83.
10. Morat: Sur l'innervation motrice de l'estomac. Lyon med., 1882, xl, 289–296.
11. v. Pfungen: Versucheuber die Benegungen des Antrum Pyloricum beim Menschen. Centralbl. f. Physiol., 1887, i, 220–223.
12. Reynolds, L., and McClure, C. W.: Motor phenomena occurring in normal stomachs in presence of peptic ulcers and its pain as observed fluoroscopically. Arch. Int. Med., 1922, xxix, 1–11.
13. Rogers, F. T.: XX. The contractions of the rabbit's stomach during hunger. Am. Jour. Physiol., 1914–1915, xxxvi, 183–190.
14. Rogers, F. T., and Hardt, L. L. J.: XXVI. The relation between the digestion contractions of the filled and the hunger contractions of the "empty" stomach. Am. Jour. Physiol., 1915, xxxviii, 274–284.

INTERMITTENT DUODENAL OBSTRUCTION IN CHILDREN*

H. Olding Foucar

Two cases of intermittent duodenal obstruction in children are presented herewith for the purpose of directing attention to the pathologic conditions found in the region of the upper gastro-intestinal tract, other than in the stomach, which may be associated with recurrent attacks of vomiting.

Case 1 (A393040). G. E. B., a boy aged four years, was brought to the Mayo Clinic for examination May 31, 1922 because of attacks of vomiting, and cough with expectoration. At the age of two years the child had contracted influenza, and one year later, acute parotitis. Four months before admission he had developed pertussis. The attacks of vomiting had begun when he was one week old and had recurred at irregular intervals, three or four times a year, each attack lasting from one to three weeks, with vomiting from two to ten times daily. The attacks were more frequent in winter. The vomiting was projectile, copious, more severe at the onset, occurred at any time of the day, and bore no relationship to meals. At first the vomitus contained food, and later a greenish mucoid material. Starvation and an oatmeal diet were the only means of relief. His last attack began March 15th, and continued for three or four days. After eating heartily for several meals, he had a return of his symptoms which were severe for about one week. This was followed by improvement, but he still vomited occasionally. He was constipated during these attacks, and had fever, the exact extent of which, however, was not known (he had none while under observation). He also complained of cramp-like aching, referred to the region of the umbilicus. A chronic cough with expectoration had been present since he contracted pertussis. At first the sputum was mucoid; later it became yellowish, thick, and increased in quantity until it amounted to almost a cupful daily for the month before examination.

General Examination.—The child was quiet, and coöperated well during the examination. His nutritional condition and muscle tone were poor. He weighed 27 pounds (normal weight for his height and age is about 33 pounds). The tonsils were enlarged, ragged, and fibrous, and there was a small pad of adenoids. The nose and ears appeared normal. There was slight enlarge-

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ment of the cervical, axillary, and inguinal lymph-nodes, and a few carious teeth. Faulty posture was evidenced by winged scapulas, a slightly protuberant abdomen, and flat feet. Unilateral bronchiectasis was found, and roentgenograms of the lungs revealed thickening and infiltration of the lower left lobe, thus supporting the clinical diagnosis. The Von Pirquet reaction was negative. Tuberculosis bacilli were not found in the sputum. The examination of the abdomen was negative.

June 1st, the child was placed in the hospital on medical treatment, and thus the bronchiectatic cavities were kept empty. As soon as his general condition permitted, it was proposed to perform a plastic operation on the wall of the chest. While in the hospital he began vomiting bile-stained fluid containing food. June 6th, the outline of the stomach was seen extending below

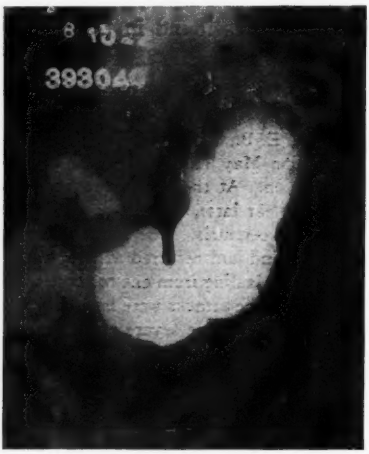

Fig. 18 (Case A393040).—Obstruction of the duodenum with dilatation of the distal portion.

the umbilicus, and a few minutes later he vomited 1250 c.c. Two days later the outline of the stomach was again noticed; it did not extend so low, but definite peristaltic waves were seen. A roentgenogram of the gastro-intestinal tract, however, did not reveal obstruction in the stomach or duodenum, although the colon was somewhat dilated. The patient was free from symptoms for six days, when they returned. Fluoroscopic examination then revealed obstruction in the duodenum about 15 cm. from the pylorus.

The question of treatment was a difficult one. Under ordinary circumstances an extensive abdominal operation would not be advisable in the face of a well-marked bronchiectasis, but the improvement of the pulmonary condition depended largely on building up the patient's general health, which was impossible on account of the intermittent attacks of vomiting.

On June 20th, Judd explored the abdomen and found that the duodenum was dilated to the upper jejunum. The small intestines were matted together by dense adhesions, and had become twisted. This volvulus, through the bands of adhesions, closed the lumen of the duodenum also. At operation the volvulus was unfolded and the adhesions freed. The child was sent home to recuperate, with instructions for the continuation of treatment of the chest. Six months later a letter was received at the Clinic stating that the child was feeling fine, was very active, and weighed 44 pounds dressed for outdoor exercise. He has not vomited since the operation, and the bronchiectasis has improved somewhat. It was advised that he return in the spring for reexamination, and probably for a plastic operation.

Comment.—The outstanding features in this case were the early onset of recurrent attacks of projectile vomiting, of large quantities of fluid, at times containing food and bile. During one attack the outline of the dilated stomach was visible and peristaltic waves passing from left to right could be seen in the epigastric region. The roentgenogram at this time revealed a definite obstruction to the duodenum.

The preoperative diagnosis was intermittent duodenal obstruction. At operation it was shown to be due to extensive chronic adhesive peritonitis. Because of the early onset of symptoms, and the absence of any postnatal illness before the onset of these symptoms, it was concluded that the child was suffering from adhesive fetal peritonitis, resulting in a volvulus of the small intestines which closed the lumen of the duodenum secondarily, resulting in intermittent attacks of obstruction. When the volvulus unfolded itself, the symptoms ceased, only to return when the mass of small intestines again became twisted on itself, and on account of adhesions closed the duodenum also. The presence of a unilateral bronchiectasis following pertussis complicated the condition.

Case 2 (A396791). J. C. R., a baby boy, aged eighteen months, was brought to the Clinic July 3, 1922, because of attacks of vomiting since birth. He had weighed 8 pounds at birth and was breast fed entirely for one year. The only infectious disease he had contracted was German measles at the age of sixteen months. When he was three days old he began to vomit three or four times daily; this persisted for three months. The vomiting was projectile and usually occurred an hour and a half to two hours after feeding; the vomitus was of greenish-yellow fluid containing very little food. Between the age of three and five months he was free from symptoms. He had gained weight since birth, but the gain was greater after three months. For the last year the weight had been stationary. When he was five months old he weighed 20 pounds clothed. He then had a severe attack of vomiting, associated with fever. This was followed by other attacks, lasting one or two days with an interval of about a week without symptoms. The vomiting had been irregular, bore no relation to meals, to the time of day, or to diet. Occasionally vomitus contained food given six hours before. The bowel movements were regular, bulky, and had a very foul odor. For the past eight months the parents had noticed wave-like movements across the upper abdomen during the attacks.

General examination revealed an undernourished child with mild rickets,

weighing 19 pounds. The abdomen was large, protuberant, and tympanitic. The liver extended 2 cm. below the costal margin in the midclavicular line. The blood count revealed mild secondary anemia. Roentgenograms of the stomach and duodenum were negative. The Von Pirquet test gave a negative reaction.

July 4th the patient was placed in the hospital for observation. He was given cod-liver oil, and a 900 calorie diet, consisting of milk, cereals, vegetables, potatoes, broths, apple sauce, and orange juice. July 14th roentgenograms taken at two-hour intervals did not reveal obstruction to the passage of food at any place in the upper gastro-intestinal tract. The child was practically free from symptoms for two weeks. July 18th he felt sick, and vomited several times. Definite peristaltic waves passing from left to right were visible in the epigastrium. A diagnosis was made of intermittent duodenal obstruction.

The child's abdomen was explored by Dr. Judd. The mesentery of the small intestines was found to be markedly edematous, but the pylorus appeared normal. The thickening of the mesentery was due to marked enlargement of the lymphatic glands. Neither bands of adhesions nor obstruction were found. The appendix was removed and also a mesenteric gland. The microscopic examination revealed a chronic inflammatory process in the appendix, and markedly inflammatory changes with degeneration in the lymph-nodes. The obstruction may have been due to some arrangement of the loops of intestines which occurred on account of the thickened edematous mesentery (Judd's surgical notes). After the operation the child had diarrhea with large, loose, slimy, undigested, foul-smelling stools, and developed acute edema of the penis and scrotum; this promptly subsided, however, and he was sent home. Three weeks later his parents wrote that the baby was apparently well, and had gained two pounds. A letter four months after operation contained the information that he had had no further attacks of vomiting, but had had considerable trouble with diarrhea.

Comment.—The chief points in this case are the recurrent attacks of vomiting, the definite peristaltic waves seen in the stomach, the absence of palpable tumor, the presence of a thickened edematous mesentery with enlarged lymph-nodes, and the presence of large, bulky, foul-smelling stools. The case is unusual, and is not easily explained. There was no dilatation. Pylorospasm must be considered, but it is unusual for this to recur so often, and yet disappear so promptly and so completely just before operation. The occurrence of peristaltic waves in the stomach indicates an obstruction high in the intestinal tract, probably in the duodenum. The mechanism in this case would seem to be transitory obstruction due to inability of the intestines to adjust themselves because of the thickened edematous mesentery.

DISCUSSION

Duodenal obstruction, acute or chronic, has been ascribed to kinking of the duodenum, owing to abnormal length, faulty rotation, or abnormal position, congenital atresia,[5, 6, 15, 17] complete or partial in any portion of the duodenum, and volvulus

of the jejunum. Constriction, due to an annular pancreas,[2] has been observed, but definite obstruction from this cause is rare. The anomaly is explained on embryologic grounds, one bud of the pancreas encircling the duodenum before it unites with the other.

In a statistical study of 262 cases of stenosis of the duodenum occurring at any age, Anders found that in 11 per cent it was due to compression of the duodenum by the superior mesenteric, or right colic arteries.[9, 10, 13, 16] This has often been described as a postoperative complication. Certain observers believe that this traction on the mesentery may be caused by visceroptosis,[19] or by a redundant cecum.[3] It is possible that the recurrent attacks of vomiting seen in children whose posture is faulty may be due to this condition. The exact place of the constriction varies according to the degree of rotation of the mesentery. Megaduodeum[7, 8, 20] has been described, but it is doubtful whether the cases reported were congenital in origin.

Congenital transduodenal bands, remnants of the fetal mesogastrium have been described by Harris and Homans.[11, 12] They rarely give rise to symptoms, however. Occasionally in adults they simulate gastric or duodenal ulcer, or chronic gall-bladder disease. Roentgenograms in such cases reveal dilatation of the first portion of the duodenum. Adhesions may arise from an old tuberculous or a septic peritonitis. I know of no other case in which duodenal obstruction arose from a fetal peritonitis. Adhesions from a pericholecystitis or scarring from gastric or duodenal ulcers hardly need to be considered in children, although they are naturally common causes in adults. Tumors, benign or malignant, arising in the duodenum, or in some adjacent organ, may produce obstruction. One case in which enlarged caseating tuberculous mesenteric glands caused duodenal obstruction has been described. In certain cases there is a dilatation of the duodenum and upper jejunum, for which no satisfactory explanation has been given.[14]

The treatment, naturally, depends on the cause. In acute gastromesenteric ileus, changing the posture so as to relieve the drag on the mesentery, and the passage of the stomach-tube, are

often effective. Duodenojejunostomy, no loop posterior gastro-enterostomy, and long loop posterior gastro-enterostomy have been advocated. Resection of the cecum or fixation of the cecum is used in certain types of chronic duodenal obstruction.[3] The good results reported by Brown and Talbot[4, 18] from correction of faulty posture by exercise, anterior-posterior pads, or spring back braces in certain cases of vomiting, may possibly be explained on the basis of release of tension on the mesentery where it crosses the duodenum.

SUMMARY

Two unusual cases of intermittent duodenal obstruction in children are reported. In the first, the obstruction was actually demonstrated to be due to an old adhesive fetal peritonitis, resulting in recurrent volvulus of the small intestines with closure of the duodenum. In the second, the obstruction was not demonstrated, but it was assumed from the case history that it was in the duodenum, and seemed to be due to the thickened edematous mesentery preventing free movement of the intestines within the abdominal cavity.

BIBLIOGRAPHY

1. Anders, J. M.: Stenosis of the duodenum; a statistical study with the report of a new case. Am. Jour. Med. Sc., 1912, cxliv, 360–369.
2. Anderson, J. H.: Abnormalities of duodenum. Brit. Jour. Surg., 1923, x, 316–321.
3. Bloodgood, J. C.: Dilatation of the duodenum in relation to surgery of the stomach and colon. Jour. Am. Med. Assn., 1912, lix, 117–121.
4. Brown, L. T., and Talbot, F. B.: The use of supports in obscure abdominal conditions. Am. Jour. Dis. Child., 1921, xxi, 347–356.
5. Cautley, E.: Duodenal stenosis. Brit. Jour. Child. Dis., 1919, xvi, 65–73.
6. Cowell, E. M.: Congenital occlusion of the duodenum. Quart. Jour. Med., 1911–1912, v, 401–408.
7. Downes, W. A.: Giant duodenum, with report of a case in a child. Ann. Surg., 1917, lxvi, 436–440.
8. Dubose, F. G.: Mega-duodenum. Surg., Gynec., and Obst., 1919, xxix, 278–281.
9. Duval, P., and Gatellier, J.: Les sténoses chroniques sous-vatériennes du duodénum par malformations congénitales du péritoine (en particulier les sténoses par compression artérielle). Arch. d. mal. de l'app. digestif., 1921, xi, 145–207.

10. Frank, E. S.: Ueber chronischen arterio-mesenterialen Verschluss des Duodenums im Kindesalter. Ztschr. f. Kinderh., 1913, ix, 99–103.
11. Harris, M. L.: Constrictions of the duodenum due to abnormal folds of the anterior mesogastrium. Jour. Am. Med. Assn., 1914, lxii, 1211–1215.
12. Homans, J.: A study of the symptoms and treatment of congenital transduodenal bands. Boston Med. and Surg. Jour., 1916, clxxv, 665–673.
13. Jewesbury, R. C.: Two cases of duodenal obstruction in infants. Proc. Roy. Soc. Med. (Section for the study of disease in children), 1922, xvi, 10–14.
14. Judd, E. S.: Pathologic conditions of the duodenum. Journal-Lancet, 1921, xli, 215–220.
15. Kreuter, E.: Die angeborenen Verschliessungen und Verengerung des Darmkanals im Lichte der Entwichlungsgeschichte. Deutsch. Ztschr. f. Chir., 1905, lxxix, 1–89.
16. Laffer, W. B.: Acute dilatation of the stomach and arteriomesenteric ileus. Ann. Surg., 1908, xlvii, 390–416; 532–557.
17. Ritter, C.: Zur Entstehung der angeborenen Duodenal-atresie. Jahrb. f. Kinderh., 1920, xci, 369–381.
18. Talbot, F. B., and Brown, L. T.: Bodily mechanics. Its relation to cyclic vomiting and other obscure intestinal conditions. Am. Jour. Dis. Child., 1920, xx, 168–187.
19. Vanderhoof, D.: Dilated duodenum with especial reference to chronic duodenal obstruction in visceroptosis. Jour. Am. Med. Assn., 1917, lxix, 510–515.
20. Variot, G., and Cailliau: Mégaduodénum congénital avec rétrécissement allongé de la troisième et de la quatrième portion du duodénum chez un nourrison. Bull. et mem. Soc. med. d. hôp. de Par., 1922, xlvi, 158–162.

JAUNDICE IN SURGICAL CHOLECYSTITIS WITHOUT STONES

HOWARD R. HARTMAN

THE history or presence of jaundice is often a deciding factor in diagnosis. When properly evaluated, its importance is not to be minimized, particularly when surgical interference of the gallbladder is under consideration. Such evaluation begins by the exclusion of hemolytic icterus with the presence of a definite excess of bile in the urine, and the absence of bile in the stool. If these conditions are present we know we are dealing with a deficient elimination of bile by the biliary system. The liver itself may be the offending organ. A hepatogenic jaundice could be a portal or a biliary hypertrophic cirrhosis, or catarrhal. Portal cirrhosis would include those cases primarily splenic, with enlarged liver, early ascites, and late jaundice described by W. J. Mayo, and those cases of liver impairment, due to toxic effects of a purely chemical nature such as chloroform and arsenic, and last to the effect on the liver of systemic bacterial toxins. Biliary cirrhosis with early jaundice and late ascites, being due to a thickening of the bile capillaries, presumably on an infectious basis, is probably more closely genetically related to the usual extrahepatic jaundice. Catarrhal jaundice holds a position midway between hepatic and common duct jaundice, as we are now being taught that the condition is due not only to inflammation of the common duct but also to an infection of the bile channels of the liver. Rosenow illustrates the dual infection in his experimental work on cholecystitis. In the extrahepatic origins of jaundice must be considered cholelithiasis with common duct stones, pancreatitis, cholangitis, neoplasms, and developing mechanical irregularities affecting the excretory apparatus. In the majority of cases the association

of pain with jaundice immediately places the excretory channels of the bile under suspicion. Other factors in the history and physical examination rapidly narrow the diagnosis to disease of the extrahepatic biliary system, for in view of severe pain requiring an opiate for relief, usually sudden in onset, originating in the upper right quadrant of the abdomen with a secondary radiation to the back, limited in duration, associated with vomiting and followed by a residual tenderness, it is logical to consider cholecystitis, possibly with stones. Should this attack be followed by jaundice, there seems to be no other alternative than that the patient also has gallstones, one of which has migrated into and occluded the lumen of the common bile duct. Should the attack subside only to be repeated, and if there is an associated qualitative gastric disturbance, common to other diseases as well, characterized by flatulency, bloating and belching, and sour regurgitation after rich foods or those with residue, the diagnosis of cholecystitis with stones is more firmly established. Since this is not always the case a few statistics relative to surgical cholecystitis and jaundice in the absence of stones are presented with the hope of strengthening the recognized belief that cholecystitis does not exist without inflammatory reaction in other parts of the biliary system or in the pancreas.

During 1922, 1027 patients suffering from gallbladder disease were operated on at the Mayo Clinic. These patients had no complications demonstrable clinically, and went to operation with a general diagnosis of gallbladder disease. Six hundred fifty-two of the patients had gallstones, and of this number, 207 (31.74 per cent) gave a frank history of jaundice; a stone obstructing the duct was found in forty-one (19.80 per cent). This leaves one to assume at the operation that in the remaining obstructed cases (166) the stone had evidently worked its way through the duct and was discharged into the duodenum, provided, of course, no other mechanical occlusion of the duct was found. By comparing these remaining cases with those of jaundice without evidence of stones in the gallbladder, one is led to the possible explanation that the jaundice had nothing to do with the presence of stones. No absolute proof of this is

at hand, but the possibility is strengthened by adding these questionable cases to those of surgical cholecystitis with the associated jaundice, probably due to inflammatory reactions along the excretory biliary apparatus. Three hundred seventy-five of the 1027 operations were performed for cholecystitis without stones, and sixty (16 per cent) of these cases were definite cases of jaundice, approximately one-half as many as of cholecystitis with stones. In other words, jaundice occurs only twice as often in cholecystitis with stones as in simple cholecystitis without stones. In case of jaundice with simple cholecystitis without stones one would expect to find the reason for this jaundice at operation. There were thirteen such patients in the group, a number not sufficient from which to draw definite conclusions, but enough to show the trend of conditions. Ten (76.92 per cent) of these patients had gross pancreatitis recognized by the surgeon. Of the other forty-seven patients with a history of jaundice, only six (12.76 per cent) had pancreatitis. This could be considered a residue of what had once been a sufficient lesion to cause an obstruction of the common duct as it passed through the pancreas. In the remaining cases of cholecystitis with jaundice and without pancreatitis, the jaundice may possibly be explained by a completely subsided or overlooked pancreatitis, or by the other factors which no doubt play a part in the production of jaundice, such as hepatitis, cirrhosis, cholangitis with occluded lumen of the ducts, and plugs of mucus. In this group, in common with all cases of cholecystitis of varying frequency, pathologic processes were often noted by the surgeon (Table 1). Pancreatitis was found in 12.96 per cent of the cases of surgical cholecystitis without jaundice (thirty-eight of 315 cases). Such a condition has potentialities of jaundice. It is not startling to note that jaundice is due to pancreatitis. The point under surveillance is that cholecystitis exists not as an inflammation of the gallbladder alone, but as only part of a general infection of the biliary tract. The sixty cases of surgical cholecystitis without stones and with jaundice came to operation not only because of the jaundice, but because of intense pain; yet at operation no stones

were found, and only seldom did the surgeon find gross changes along the biliary tract. Pain no doubt was an important factor in deciding the operative interference, for in twenty-four cases (40 per cent), gallstones were diagnosed, and in eight, obstruction of the common duct, implying stones. The remaining twenty-

Table 1

A comparison of clinical diagnosis with surgical findings in sixty cases of surgical cholecystitis without stones and with jaundice classified according to the time of jaundice in the history

	Clinical diagnosis					Surgical findings										
	Cases	Cholecystitis	Cholecystitis and common duct obstruction	Cholecystitis and cholelithiasis	Common duct obstruction	Dilated ducts	Enlarged glands along ducts	Pancreatitis	Hepatitis	Cholangitis	Cirrhosis of liver	Thick-walled gallbladder	Bile in gallbladder and ducts	Strawberry gallbladder	Papilloma	Adhesions
Ancient jaundice	22	12	1	9	0	1	5	4	6	1	3	5	3	5	5	7
Recent jaundice	25	13	0	12	0	1	9	2	4	0	0	5	4	11	5	6
Present jaundice	13	3	3	3	4	5	7	10	4	2	1	4	4	2	2	3
Total	60	28	4	24	4	7	21	16	14	3	4	14	11	18	12	16

Table 2

Cardinal signs and symptoms in sixty cases of surgical cholecystitis without stones and with jaundice

	Cases	Per cent	Without pain	Repeated attacks	Following pain	Repeated attacks	Degree of pain					Degree of jaundice				Average duration of jaundice, days
							Grade 1	Grade 2	Grade 3	Grade 4	No pain	Grade 1	Grade 2	Grade 3	Grade 4	
Ancient jaundice	22	36.66	6	1	19	6	5	2	5	9	1	14	3	3	2	28.20
Recent jaundice	25	41.66	2	0	23	13	5	10	2	7	1	23	2	0	0	6.42
Present jaundice	13	21.66	2	1	11	4	5	2	0	4	2	5	4	4	0	29.50
Total	60		10	2	53	23	15	14	7	20	4	42	9	7	2	21.86

eight were called cholecystitis, a term sometimes loosely applied, meaning that the condition is of surgical importance, and showing an indifference to the probability of gallstones. Clinicains fully aware of the "silent gallstones," subconsciously associate gallstones with pain. An analysis of the degree of pain in these

sixty cases shows that, in twenty (33.3 per cent), it is of Grade 4 (requiring morphin); in seven, it required the attention of a physician (Grade 3); in fourteen, the patients were incapacitated for the time, and local measures were used (Grade 2), and in fifteen, the pain was mild, but definite enough for distinct localization (Grade 1). The average duration of the jaundice was twenty-one and eight-tenths days. The cause of the pain, particularly when severe and simulating the acute pain of gallstone colic, as it did in these cases of cholecystitis and jaundice without stones, can only be surmised. From the fact that jaundice followed pain in fifty-three of the sixty cases (88.3 per cent), and that in 76.92 per cent of the cases in which operation was performed during jaundice there was pancreatitis, it would seem that the associated pancreatic disease played a definite part in causing the pain, so-called "pancreatic colic." Obstruction of the duct to the liver may cause the pain in pancreatitis. Hepatitis, cholangitis, and distended ducts and gallbladder no doubt are also responsible. The jaundice came as a sequela to the pain in fifty-three of the sixty cases; some of the patients had previously had painless jaundice, which may possibly be explained on a catarrhal basis.

In a classical case of gallstone pain followed by jaundice and associated with gastric disturbances, one is justified in making the diagnosis of cholecystitis with stones, but from the foregoing it may be seen that the diagnosis is not infallible. Of what importance is this to the patient? It is only that by removal of the gallbladder he is cured. Graham and Peterman, in their work on the etiology of cholecystitis, maintain that cholecystitis is preceded by, and associated with hepatitis; this dual infection being possible because of the lymphatic communication between the gallbladder and liver. Lymphatics carry the infection along the ducts to the pancreas. These observers maintain that an interchange of infection through the lymphatics from one organ to another is possible. Surgeons note this pan-inflammation, evidenced by differentiating at operation, hepatitis, cholangitis, enlarged lymphatic glands along the ducts, and pancreatitis. The removal of the gallbladder may not remove the major portion

of this infection. In the sixty cases under consideration, all the infections of the gallbladder were diagnosed by the pathologist as chronic catarrhal cholecystitis; eighteen were of the strawberry type, and twelve had gone on to the formation of papillomas. The operation cures the patient with few exceptions. To speculate on the reason for the cure, it removes a mass of infected tissue, breaks a lymphatic path, gives the patient forced rest in bed under conditions excellent for regenerating depleted resistance, and makes him careful of himself for some time to come in his postoperative convalescence, thus again adding to his resistance in combating the residual infection in the remaining biliary system and pancreas. Patients with surgical cholecystitis without stones require greater care than those with stones, because a gallbladder that harbors stones is an old offender. Inflammatory reactions here are of long standing and marked degree, and have been necessary to bring about stone formation.

During the same year (1922) 652 patients with gallstones were operated on. Jaundice was present in 207 (31.74 per cent). Thirty-five (16.9 per cent) had hepatitis; eleven (5.31 per cent) had cirrhosis; thirty-two (15.45 per cent) had enlarged glands along the bile ducts; eight (3.86 per cent) had cholangitis; fifty-eight (28.01 per cent) had pancreatitis, and forty-one (19.8 per cent) had stone of the common duct. The fact that pancreatitis was noted in 26.6 per cent of cases of cholecystitis and in 28.01 per cent of cases of cholelithiasis might seem contradictory to the discussion, but when it is shown by Graham and Peterman that there is apparently a continuous interchange of infection in the various parts of the biliary system, and when we consider that stones in the gallbladder imply a certain degree of chronicity in the inflammatory process, and thus an opportunity for the development of a pan-biliary infection by the means suggested, we should expect to find chronic pancreatitis quite prevalent in cases of cholelithiasis, particularly when we know that gallstones do not form in a healthy gallbladder.

If there were any rational treatment other than surgery for cholecystitis, one might try it even in the presence of gallstone-

like attacks with jaundice, because it does seem that it might be possible to rid the patient of this bacterial invasion without surgery. Natural processes care for typhoid, pneumonia, and the like, but the nature of the organisms causing biliary infection makes it possible for them to continue their havoc for years. In the future, when antibodies are prepared against these organisms, there may be a specific nonsurgical method of attack, but in the meantime we must rely on major surgery, in addition remove all possible sources of primary infection, such as diseased appendix, infected teeth and tonsils, and drain infected accessory nasal sinuses. Prevention of reinfection of the biliary system by the removal of occult or frank foci throws less strain on the general body resistance, and brings on a more rapid and satisfactory cure.

SUMMARY

Jaundice in surgical cholecystitis is often erroneously diagnosed as cholecystitis with stones or obstruction of the common duct. The pain, its character, location and degree, followed by jaundice, leads one into error. The etiology of the jaundice is explained by pancreatitis as definitely as the surgeon is able to determine, and the pain usually by pancreatic colic. All disease of the gallbladder is a pan-biliary infection. Removal of the gallbladder frees the patient from a part of the pathologic process, but never does it remove all the infectious processes. At present surgery is the rational treatment, because it removes a mass of infected tissue and automatically makes possible an augmentation of resisting powers to the residual infection. The necessity of removal of primary foci cannot be overlooked.

DUODENAL ENZYMES IN CHRONIC ULCERATIVE COLITIS

PHILIP W. BROWN

THE numerous difficulties and problems in the study and treatment of chronic ulcerative colitis, and the question of the etiology of many of the indeterminate diarrheas, led to a study of the enzymatic activity of the duodenal contents of these patients in the hope that it might be ascertained, whether there is an increased or a decreased action of the enzymes, and that the theory of an insufficiency of the secretions of the upper intestinal tract might be corroborated or disproved.

As controls several patients were studied whose condition had been diagnosed "indeterminate diarrhea," "sprue (?)," "chronic pancreatitis (?)." I shall not discuss chronic ulcerative colitis as such, but refer the reader for information on this subject, to the comprehensive article by Logan in 1919.

Krieger, in 1921, used the Gross and Wohlgemuth casein and starch methods, and his own monobutyric acid method for lipase in studying the enzymatic action of seventy-three cases, which included normal controls, cholecystitis, diabetes and achylia. Gyotoku, in 1922, used the same general methods in a study of the duodenal enzymes in Graves' disease. Both sets of tables show variations, but none of these permit definite conclusions. It is possible that this uncertainty of the results can well be accounted for on the probable action of the succus entericus, and perhaps also of ptyalin. Peptic digestion need not be taken into consideration, as a hydrogen-ion concentration of 8.4 is sufficient to inhibit action of the pepsin.

In chronic ulcerative colitis there is a marked hyperperistalsis of the entire gastro-intestinal tract. Patients on whom a

modified Brown ileostomy has been performed often observe that food such as pickles will appear at the ileostomy opening, thirty to forty minutes after ingestion. The rapid peristaltic contractions of the proximal segment are visible, and at times the wave seems to "carry on" with the peristaltic wave appearing in the distal segment, apparently indicating that the wave of peristalsis is a nerve impulse; a nerve reflex not dependent on the continuity of the bowel wall, but initiated high up in the intestinal tract and carried by a continuous reflex down through the bowel. At times the liquid contents of the ileum come out in spurts of 30 to 40 cm. Associated with this hyperperistalsis and liquid ileal content, there is intense redness and burning, even to the stage of ulceration, wherever the discharge comes in contact with the skin. This excoriation may spread over the entire abdomen and down the thighs. It seems to be a digestion of the skin by the ileostomy secretion, very similar to the irritation which occurs around a duodenal fistula. The patients complain bitterly of the burning and soreness, and these symptoms constitute a distressing complication.

The clinical observations led to the idea that the intestinal juices might be hyperactive, or that the rapid peristalsis was delivering the normal juices into that portion of the bowel which is not accustomed, on an embryologic basis, to such high enzymatic concentrations. In the normal individual it takes four to six hours for food to reach the ileocecal valve, and twelve to twenty-four more hours for it to be evacuated. In ulcerative colitis, food and intestinal juices are delivered to the colon within an hour, and in some instances the meal is passed from the rectum within two hours from the time of ingestion.

Recent investigators of duodenal contents object to estimations made on the activity of enzymes in the feces. The possibilities of error are obvious. Hence, a satisfactory method of making such estimations was sought. After the trial of several proposed methods, including those of Buckstein, Einhorn, and Gross and Wohlgemuth, the method of McClure, Wetmore, and Reynolds was found to be the most accurate. It seems more nearly to duplicate physiologic conditions, and also gives results

expressed in terms of quantitative chemical determinations. This method was used except that lipase determinations were not made. A finely divided oil emulsion was not available for these studies; the monabutyric acid method of Krieger will be tried in further studies. However, it is hard to conceive that there is such a selective activity of the pancreas which would cause it to secrete amylase and trypsin in normal or abnormal amounts, and not have a corresponding secretion of lipase. Friedenwohl and Sindler's work does show a tendency toward selective secretory activity; further work on this phase is necessary.

In preparation for the test patients had their usual evening meal the day before the examination, after which nothing was allowed but water or plain tea, which were permitted since it has been found easier to pass the stomach-tube if the patient has had some fluid. The tube was passed at eleven a.m.; as soon as it was definitely in the duodenum, a specimen was taken, and in all but one case it was clear golden yellow, with the consistency of strained honey. Forty cubic centimeters of cream were given, and another specimen was removed at the end of an hour. The contents were now a light yellow, and very viscid, even clotted at times. The condition of the patients did not permit the tube to be retained longer than one hour after the test-meal was given. Hydrogen-ion determinations were made as soon as the specimen was obtained. The contents were dialyzed through a collodion sac against double distilled water, and the indicator method of Clark used. This is an adaption of Rowntree's method for hydrogen-ion concentration in the blood. The results are recorded in Table 1. The figures are the average of two determinations, which were very close in each case; the controls are also deducted. There was always some sugar reduction in the starch solution, but the controls in the casein were negative, or revealed only a very faint trace on nesslerization.

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Table 1

Determinations of the enzymatic activity of the duodenal contents

Cases	Diagnosis: ulcerative colitis	After eighteen hours' fast			One hour after cream meal		
		Hydrogen-ion concentration	Non-protein nitrogen, mg.	Sugar, mg.	Hydrogen-ion concentration	Non-protein nitrogen, mg.	Sugar, mg.
1	Active	7.8	?	2.5	8.2	4.6	3.5
2	Active	7.4	1.56	2.3	6.8	2.2	6.4
3	Active	4.2	1.28	1.0	2.6*	1.3	1.0
4	Active	7.2	4.4	4.84	6.6	3.6	3.8
5	Active	8.4	1.44	0.73	7.0	1.65	3.1
6	Active	7.2	3.8	1.52	3.0*		
7	Subsiding	7.4	1.8	2.8	6.8	2.2	1.5
8	Subsiding	7.2	0.6	2.24	8.4	Trace	2.28
9	Quiescent	4.6	Trace	1.3	7.4	1.74	2.2
10	Indeterminate (?) diarrhea (sprue)	8.0	1.5	3.4	7.4	1.2	3.2
11	Indeterminate diarrhea	7.4	1.08	1.52	4.2	1.3	1.08
12	Indeterminate diarrhea		Trace	1.88		1.8	1.78
13	Chronic pancreatitis verified by operation	6.8	3.52	2.4	6.6	3.6	3.45
14	Normal	7.8	1.76	1.82	6.6	2.64	3.0
15	Normal	7.8	3.6	3.1	2.4*		
	Range of enzymatic activity in ulcerative chronic colitis						
Range for active ulcerative colitis**		7.2 to 8.4	1.44 to 3.8	0.73 to 4.8	6.6 to 8.2	1.3 to 4.6	2.2 to 6.4
Average range for active ulcerative colitis**		7.4	2.8	2.97	7.1	3.0	4.2
Normal range (McClure)			1.2 to 5	0.3 to 6.7	5 to 7.5	0.8 to 4.3	0.0 to 3.1

* Gastric contents present (?)
\- Mucus in excess
** Omitting those in which there was gastric contents

Table 2

Comparative analysis of enzymatic activity of contents of duodenum and lower ileum

Duodenal contents: After eighteen hours' fast			Duodenal contents one hour after meals			Ileostomy discharge		
Hydrogen-ion concentration	Non-protein nitrogen, mg.	Sugar, mg.	Hydrogen-ion concentration	Non-protein nitrogen, mg.	Sugar, mg.	Hydrogen-ion concentration	Non-protein nitrogen, mg.	Sugar, mg.
7.4	1.56	2.3	6.8	2.2	6.4	7.4	1.35	5.1

DISCUSSION OF RESULTS

The hydrogen-ion concentration was fairly constant throughout, except in a few spedimens in which it seemed evident that there was more gastric than duodenal content. Retching while a specimen is being aspirated will be certain to cause the material to become strongly acid. After digestion, the tendency is

toward the more acid reaction. A hydrogen-ion concentration of less than seven* in the intestine has been the finding of McClendon, McClure, and others. This is further evidence that the reaction in the intestine is on the acid side of neutrality, which disproves the former believe that the reaction in the bowel is alkaline.

The proteolytic action varied in the cases of ulcerative colitis; three of the six active cases showed rather high non-protein nitrogen values. Two cases diagnosed chronic pancreatitis, or pancreatic insufficiency, gave low figures. The possible sprue case showed the same result. Manson also has referred to a pancreatic insufficiency in sprue.

The amylolytic activity showed a tendency to be more marked in the active cases of ulcerative colitis. Values approaching the low normal were present in the subsiding and quiescent cases. In the four cases of "pancreatic insufficiency," results were variable. The outstanding feature of the enzymatic activity in ulcerative colitis is that the results obtained show higher values than McClure has found in specimens removed one hour after the test meal. This would indicate that the activity of the ferments is not only sufficient, but that it borders on the hyperactive. In the cases of active colitis, the activity of the enzymes is more marked. The hyperperistalsis of the active stage delivers more powerful enzymes into the colon, possibly an important factor in causing the extensive ulceration. In one case in which clinical symptoms of a pancreatitis had been demonstrated at operation, both the proteolytic, and amylolytic activity was high. It is in a case such as this that many of the factors which influence enzymatic activity come to light. The laboratory tests can well be harmonized theoretically on the following grounds: Morgagni experimented on the effect of hydrochloric acid on ptyalin; his experiments indicate that the activity of ptyalin is not destroyed in the stomach, but merely inhibited, and on its arrival in the intestine its amylolytic action is resumed. If this is correct, the test-tube of starch with a

* The value seven stands for neutrality. Below seven is acid, and above it is alkaline.

hydrogen-ion concentration of 8.4 offers an optimal medium for ptyalin activity, and affords excellent opportunity for further amylolytic action. Euler, quoting Nagayarma, says that erepsin does not act on any native proteins except casein. Casein is the digestion mixture used; and furthermore, the optimum for erepsin activity is afforded by the temperature of forty degrees, and the hydrogen-ion concentration of 8.4. This one case does not permit conclusions, and yet emphasizes the fact that, in interpreting estimations of the enzymatic activity of the duodenal contents, it must be thought of in terms of proteolytic and amylolytic activity, and not in terms of amylopsin and trypsin.

In one case of my series in which a modified Brown ileostomy had been performed for active chronic ulcerative colitis, there was marked digestion, or erosion of the abdominal wall as a result of the liquid ileal discharge. Some of the liquid discharge was collected in a special tube at the time of the withdrawal of the second specimen from the duodenum, and the enzymatic activity estimated in 1 c.c. of the material, as in the routine method for the duodenal contents.

The foregoing data would seem to indicate that the enzymatic activity of the bowel contents at the ileocecal valve corresponds to that of the duodenal contents. The evidence of a potent duodenal secretion which maintains its high enzymatic activity on reaching the ileocecal valve readily explains the skin digestion; its relation to the creation, or aggravation of diffuse ulceration of the colon is a point which may be discussed further.

SUMMARY

1. The enzymatic activity of the duodenal contents in cases of ulcerative colitis is high, on the basis of McClure's reports. In active cases this activity is more marked, and conversely, decreased as the condition subsides.

2. There is evidence that a "normal" enzymatic activity may exist in the presence of chronic pancreatitis.

3. It is important to note that the activity, and not the amount of the enzymes is estimated. Furthermore, the results

should be expressed in the general terms of "proteolytic" or "ameolytic" activity, and not as due only to trypsin or amylopsin.

4. One case of ulcerative colitis demonstrated that the enzymatic activity at the ileocecal valve is practically as powerful as it is in the duodenum. This explains the skin digestion in the patients with ileostomy, and may be the factor causing the ulceration, if a decreased resistive power in the colon wall is assumed.

BIBLIOGRAPHY

1. Buckstein, J.: Direct determination of lipase within the small intestine: a test for pancreatic function. Jour. Am. Med. Assn., 1922, lxxix, 1766–1767.
2. Clark, W. M.: The determination of hydrogen ions. Baltimore, Williams and Wilkins, 1920, 38–43.
3. Einhorn, M.: The duodenal tube and its possibilities. Philadelphia and London, Saunders, 1920, 42–44.
4. von Euler-Chelpin, H. K.: General chemistry of the enzymes. New York, Wiley, 1912, p. 38.
5. Friedenwald, J., and Sindler, J.: Fractional analysis of the duodenal contents in normal individuals. Jour. Am. Med. Assn., 1921, lxxvii, 1469–1471.
6. von Gross, O.: Zur Funktionsprüfung des Pankreas. Deutsch. med. Wchnschr., 1909, i, 706–708.
7. Gytoku, K.: On the amounts of enzymes in duodenal fluid in Graves' disease. Japan Med. World, 1922, ii, 339–343.
8. Hawk, P. B.: Practical physiological chemistry. 7 ed. Philadelphia, Blakiston, 1921, 195–196.
9. Krieger, K. I.: Zur quantitativen Bestimmung der Fermente im Duodenalsaft. Ztschr. f. klin. Med., 1921, 259–268.
10. Levy, R. L., Rowntree, L. G., and Marriott, W. M.: A simple method for determining variations in the hydrogen-ion concentration of the blood. Arch. Int. Med., 1915, xvi, 389–405.
11. Logan, A. H.: Chronic ulcerative colitis. A review of 117 cases. Northwest Med., 1919, xviii, 1–9.
12. Maestini-Morgagni, D.: The activity of alimentary substances and the activity of ptyalin in acid medium. Internat. Med. and Surg. Survey, 1922, iii, 829.
13. Manson, P.: Tropical diseases. A manual of the diseases of warm climates. London, Paris, and New York, Cassell, 1898, 322–340.
14. McClure, C. W., Reynolds, L., and Schwartz, C. O.: On the behavior of the pyloric sphincter in normal man. Arch. Int. Med., 1920, xxvi, 410–430.
15. McClure, C. W., and Wetmore, A. S.: Physical characters and enzymatic activities of duodenal contents. Jour. Am. Med. Assn., 1921, lxxvii, 1468–1469.

16. McClure, C. W., and Wetmore, A. S.: Studies in pancreatic function. Enzyme concentration of duodenal contents after the ingestion of pure food-stuffs and food mixtures by normal men. Boston Med. and Surg. Jour., 1922, clxxxxvii, 882–895.
17. Myers, F. J., and McClendon, J. F.: Note on the hydrogen-ion concentration of the human duodenum. Jour. Biol. Chem., 1920, xli, 187–190.

THREE CASES OF CHRONIC ULCERATIVE COLITIS CURED BY IODIN

A. H. Logan

The three cases under discussion fall in the group of chronic ulcerative colitis for which we have been unable to find a specific cause. Many organisms, such as the colon bacillus, streptococci, the dysentery bacilli, the ameba, and several others have been named by various authors as the cause, but general confirmation has been lacking. The multiplicity of suggested causes argues against any one specific cause. I have come to the conclusion that the bacteria and parasites are secondary invaders of the walls of the colon, due to a lowering of tissue resistance because of a change in some of the normal secretions of the body. Whether such change takes place in the digestive juices of the upper gastro-intestinal tract, or in the endocrine secretions, is not clear. A few patients recover spontaneously; most other reported cures have resulted from the subcutaneous or intravenous injections of a foreign protein in the form of a specific vaccine.

Sterilizing the colon has not resulted in healing the ulceration. In one instance, after ileostomy 6 inches above the ileocecal valve (modified Brown operation), and bringing both ends of the ileum to the outside, the bowel was irrigated with normal salt solution, acriflavin, silver nitrate, and various other drugs, with the result that on three successive days sterile cultures were obtained from the distal ileostomy, and from the rectum, but without healing in the colon.

In numerous other cases the activity of the inflammation, and the ulceration in the rectum and colon, can be judged by the character of the intestinal discharge from the small intestine. In certain cases, after an ileostomy of the type described, there

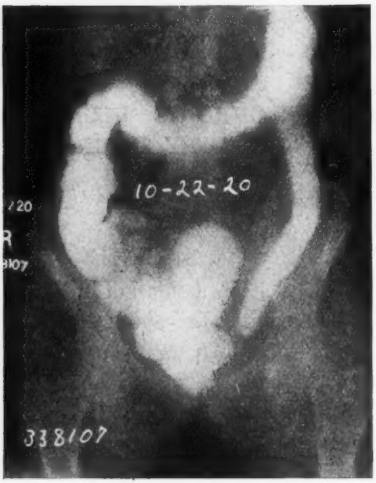

Fig. 19.—Left colon straight, narrow, and not haustrated.

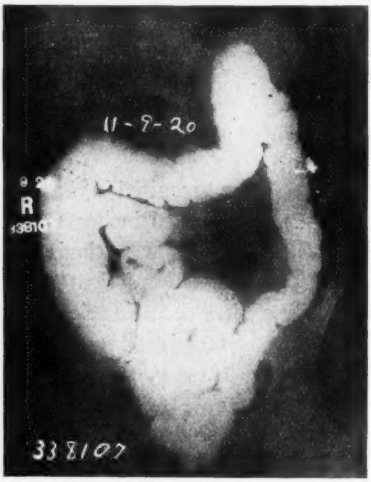

Fig. 20.—Same case as Fig. 19. Eighteen days after institution of iodin treatment. Bowel normal.

Fig. 21.—Irregular angular haustra, showing evidence of inflammation of colon.

Fig. 22.—Same case as Fig. 21. Two months after institution of iodin treatment. Bowel normal except for slight deformity in cecum.

Fig. 23.—Typical picture of chronic ulcerative colitis.

Fig. 24.—Same case as Fig. 23. Three weeks after institution of iodin treatment. Bowel normal.

are periodic discharges from the proximal ileostomy of a very irritating watery fluid which digests the skin and subcutaneous tissues with which it comes in contact. It acts similarly to the digestion around a duodenal fistula, except that the fluid comes in enormous quantities, and seems to be more active than even the normal duodenal contents, although this may be due to the large quantity. Peristalsis is very active, the fluid at times squirting a foot from the opening. During this period of exacerbation, although none of the fluid reaches the colon, the proctoscope in the rectum reveals very active inflammation, and there are frequent passages of pus, blood, and serum.

It thus seems probable that a general metabolic disturbance is responsible for the trouble. At the start the protective mechanism is broken down, and later toxins from any infection are sufficient to start an exacerbation. The most common cause of exacerbation is acute rhinitis or acute respiratory infection.

About three years ago Dr. J. F. Robinson, who had been stationed in India during the war, told me that many drugs had become exhausted there, and he had used tincture of iodin by mouth in many gastro-intestinal disorders, with surprisingly good results. I decided to try it in chronic ulcerative colitis, and happily chose a case in which, to our surprise, a complete cure was effected in three weeks' time. Since then cures have been effected in two other cases with iodin. Iodin has been of great benefit in many cases, but of no value in others.

REPORT OF CASES

Case 1 (A338107). E. L., a Russian Jewess, aged twenty-two years, was examined in the Mayo Clinic October 18, 1920. One year before she had had an attack of diarrhea lasting one week; there had been slight abdominal pain, but no blood was passed. During the next six months she was constipated and occasionally passed a little blood; she then had been confined to bed for six weeks with severe diarrhea, and had passed much blood and mucus. The third exacerbation started three weeks before her examination, with severe colicky abdominal pain, and the passage of much blood and pus in the stools. She had had six stools during the day and seven at night. Everything eaten passed rapidly through the gastro-intestinal tract, but no one article of diet seemed to effect the diarrhea. The patient lost strength rapidly.

The hemoglobin was 57 per cent; the erythrocytes numbered 3,800,000, leukocytes 10,800, polymorphonuclears 44, small lymphocytes 37.5, large lymphocytes 8.5, eosinophils 9.5, and basophils 0.5. The Wassermann reaction on the blood was negative. Two stool examinations revealed blood, mucus, and pus, but were negative for parasites, ova, or the bacillus of tuberculosis. The proctoscope revealed a markedly granular mucous membrane, which bled on the slightest trauma, very severe scarring, and a posterior anal fissure; this condition extended into the colon. Roentgenograms of the colon revealed the characteristic deformity in the left half of the colon, which is seen in chronic ulcerative colitis. October 22d 10 drops of the tincture of iodin three times a day was given by mouth, following which there was progressive improvement. November 6th the proctoscopic report read: "The rectal mucosa is pitted with numerous pinhead scars which were the granular areas October 21st. The bowel is negative otherwise. The easy traumatic hemorrhage noted at first examination has disappeared. The bowel was examined for 26 cm." November 9th the patient was dismissed from observation feeling well, and having one formed stool daily. Roentgenograms of the colon on this date showed a normal bowel.

Case 2 (A405063). G. R., a man aged thirty-four years, was examined September 18, 1922. One and a half years before he had noted fulness and bloating in the left lower abdomen, with normal stools, but inability to expel gas. Suddenly, in December, 1921, diarrhea started with from two to four bowel movements daily, containing blood and mucus. Exacerbations occurred with from six to eight liquid stools and tenesmus. There was no abdominal soreness. The patient's appetite was good, but he lost twenty-three pounds in weight in the first three months. Just before coming to the Clinic his condition was diagnosed malignant tumor high in the rectum.

The hemoglobin was 71 per cent; the erythrocytes numbered 4,390,000, and the leukocytes 11,600. The differential count was normal. The Wassermann reaction on the blood was negative. Three stool tests were negative for parasites, ova, and typhoid and dysentery bacilli. Culture revealed many streptococci. The proctoscope revealed scattered linear and round areas of ulceration covered with a grayish membrane extending up to the third valve. The intervening mucous membrane was a healthy pink. The condition appeared to be chronic ulcerative proctitis in a period of remission. Roentgenograms of the colon were suggestive of chronic ulcerative colitis. The patient was unable to remain for treatment, and was placed under the care of his home physician, tincture of iodin, 10 drops three times daily being prescribed, with rectal irrigations of hot sodium chlorid solution and injections of argyrol and witch hazel. He returned for examination February 12, 1923. There had been no blood in the stool for one month. Treatments had been stopped two weeks before. Two stools and some mucus were being passed daily. The patient had regained his weight, but had some insomnia. The proctoscope revealed a normal bowel for 24 cm. Roentgenograms of the colon revealed the left half to be normal, but some deformity was still evident in the right half.

Case 3 (A415864). A woman, aged fifty-one years, came to the Clinic as an emergency case January 19, 1923. She had had bilious attacks all her

life, together with diarrhea and occasional vomiting. In the last few months her bowels have moved more frequently. Five days before she began vomiting, and had severe diarrhea, with blood in the stools and severe griping pain in the rectum. Stools of a bloody serous character passed every hour with extreme urgency. A diagnosis of carcinoma of the rectum was made elsewhere on proctoscopic examination.

The hemoglobin was 63 per cent; the erythrocytes numbered 4,020,000. and the leukocytes 6800. The Wassermann reaction on the blood was negative. One stool test demonstrated pus and blood in excess, but no parasites or ova. The proctoscope revealed diffuse ulceration which showed some effects of healing. The ulceration extended throughout the rectum and sigmoid. There was relatively little bleeding for the amount of ulceration. The ulceration was not the moth-eaten type, but more scattered, and covered by membranous bases linked together. The whole lumen of the bowel was contracted about one-third. Roentgenograms of the colon disclosed the deformity of chronic ulcerative colitis throughout.

The patient was placed on tincture of iodin 10 drops three times daily by mouth, and was given seven rectal injections of 20 c.c. of witch hazel. February 12th the proctoscope showed that the bowel was normal with all ulcers healed. Roentgenograms revealed that the colon was normal.

DISCUSSION

What is the effect of the tincture of iodin in these cases? Is its effect local on the colon mucosa, or by absorption on general metabolism? Tincture of iodin is five-twelfths potassium iodid and seven-twelfths iodin. In three patients with the disease, iodin, equivalent to that present in potassium iodid was recovered from the urine; thus a general effect was given and yet iodin was left in the intestinal contents for local action. A saturated alcoholic solution of iodin crystals, with dosage equal to double the amount of tincture of iodin was given, and iodin was obtained from the urine equivalent to that obtained when using the tincture. Tincture of iodin was given by mouth to one patient having an ileostomy, and in a few hours a severe iodin dermatitis around the ileostomy resulted, and at the same time the urine returned the equivalent amount of potassium iodid in the iodin given.

Irrigations of the ulcerated colon with iodin cause severe cramping pains unless the iodin is very dilute, and do not seem to exert any more beneficial effect than other irrigations. But in all cases in which iodin was given by mouth, either as tincture

or as the saturated solution of iodin crystals, the effect was both local and general; whereas local irrigations produced only a local effect. It is true that the iodin, when given by mouth, was applied more constantly to the mucosa than by irrigation. The noticeable effect in all cases in which the healing was partial or complete, was that the patient noticed and spoke of feeling so much better within twenty-four hours. Also, that in two of the three cases reported, healing was complete in three weeks. I feel that we are justified in assuming that the result came through a general metabolic change, rather than local effect. Why benefit was derived in only three of the many cases in which the treatment was tried, I am unable to determine.

In a number of cases there was an immediate response for from five to seven days; the abdominal pain stopped, and the stools decreased from seven to twelve to two or four in twenty-four hours. But, after this immediate improvement, there was always a return of the trouble.

Attention is directed to the return of the colon to normal as evidenced both by roentgenographic and proctoscopic examination. We have had a few spontaneous recoveries with the same result in which such an outcome, on our first examination, seemed impossible. In the larger number of cases, however, after long and patient treatment, or no treatment, a scarred and deformed colon remains. The complete return to normal in the cases reported confirms the theory of secondary infection, which a return of the protective mechanism to normal overcomes to a large extent.

THE IMPORTANCE OF PROCTOSCOPIC EXAMINATION

LOUIS A. BUIE

PATIENTS with rectal trouble have too long presented their complaints and received treatment without investigation. Pills, pile ointments, suppositories, and so forth, have been prescribed ad libitum, and patients have reported at hospitals, dispensaries, or clinics late in the course of the disease. It happens often that a hemorrhoid operation is the means of diagnosing cancer of the rectum, much to the operator's surprise. It is sometimes necessary, in indefinite abdominal conditions, to explore after all means of diagnosis have been exhausted, but since proctoscopy is so simple, there is no excuse for waiting until a hemorrhoid operation is in progress in order to examine the rectum above the hemorrhoidal area for malignancy.

Very few cancers present themselves in a manner to be discovered early by the patients; more than 90 per cent are hidden, and their presence is suggested only by signs which occur in the advanced stages of the disease. It is appalling how many patients come to hospitals and clinics, with rectal or sigmoidal cancer, very often inoperable, complaining of symptoms which they have endured for months, and who have had recent operations for hemorrhoids. The interpretation is obvious; the patient was finally operated on for hemorrhoids without a thorough examination, and the malignant lesion found during the operation.

A patient recently came to the Clinic for examination and gave a history of bleeding piles of a year's duration. He had consulted a physician when the bleeding began, and had been receiving treatment for bleeding hemorrhoids. Two weeks before coming to the Clinic, annoyed by the continued bleeding,

and suffering a new discomfort, pressure in the lower rectum, he had inserted his own finger and felt a mass. When I examined him, I found a huge, fixed, inoperable cancer within easy reach of the finger.

The chief difficulty is that the first visit of a patient having rectal symptoms usually ends with a prescription for a dose of salts, and salve for local application. He is instructed to return in a few weeks if he is no better. Invariably he finds it necessary to return. Often the same program is repeated; perhaps a pill or a pile ointment is ordered, and the patient is allowed to go away again. This is so different from the method of caring for patients with other disorders. Stethoscopes, auroscopes, and ophthalmoscopes are used excessively; the teeth, tonsils, throat, heart, lungs, stomach, in fact, all the other organs of the body are examined exhaustively with innumerable diagnostic machines; but as soon as rectal complaints are presented, there develops an involuntary antipathy on the part of the examining physician, and the trouble is not relieved, and often is not looked for.

With very little practice any medical, surgical, or general practitioner should be able to use the proctoscope intelligently. I do not believe that one untrained in its use should attempt to pass the proctoscope into the sigmoid, nor should he use it for therapeutic purposes, but the rectum in its entirety can be explored with relative ease and with little or no discomfort experienced by the patient.

EQUIPMENT

There are many types of proctoscopes. The one shown in Figure 25 (1) with its obturator in Figure 25 (3) has been modeled after the Beach instrument, and is quite satisfactory for the work at the Mayo Clinic. It is 1.56 cm. in diameter and 25 cm. in length. The light is in the end of the scope farthest from the examiner's eye and nearest the object to be studied. The light carrier passes through the barrel of the instrument so as to do away with the ridge on the end that is inserted. This feature makes it possible to dilate the anus easily and without the pain which was caused by the uneven surface of the original instru-

ment. There is a graduated scale of inches and centimeters on the barrel which aids in locating lesions accurately. A flange on the end presents a rounded border instead of a sharp edge and makes injury to the mucosa of the bowel less likely.

The lights are very delicate and a rheostat attachment on a regular city current burns them out too frequently; we have, therefore, employed dry cells. A very useful battery is shown in Figure 25 (6) and its wire coil in Figure 25 (7). The fillers are easily obtained and it makes a very convenient, portable

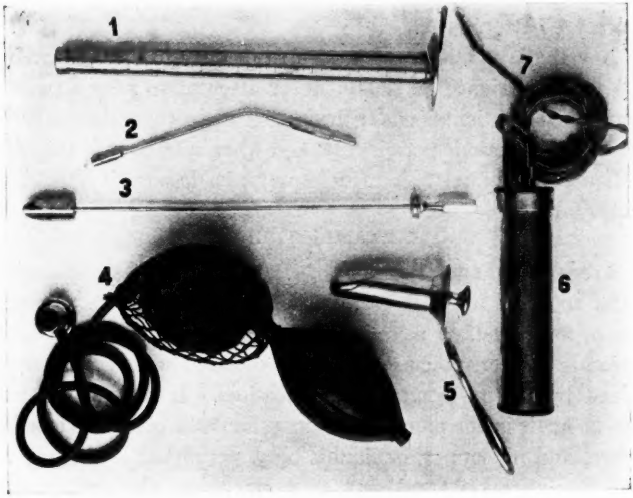

Fig. 25.—An adequate equipment for proctoscopic diagnosis.

outfit. The amount of light desired can be regulated by a small rheostat attached on top; the small light shown in Figure 25 (2) can be attached directly to the battery. Two or three larger dry cells are better if the proctoscope is used daily. It is sometimes necessary to inflate the bowel with air during the course of the examination; the bulb and tube shown in Figure 25 (4) are provided for this purpose. Inflation should seldom be necessary and extreme care should be exercised not to distend the bowel too far.

The Hirschman anoscope as shown in Figure 25 (5) is an instrument of the utmost value. With it the anus and lower rectum can be examined most satisfactorily. The light in Figure 25 (2) should be used with the anoscope, and I have, under favorable conditions, been able to examine the rectum up to the rectosigmoid with these appliances.

It is often necessary to swab away feces, blood, mucus, and so forth, and for this purpose a supply of cotton applicators should be provided. Soap should not be used as a lubricant; vaselin is satisfactory, but there are many water-soluble lubricants which are better.

Anesthesia is seldom necessary, and unless the examiner has had vast experience he should never attempt to pass a proctoscope when a patient is under the influence of a general anesthetic. A local anesthetic is permissible, and when a patient is suffering with a painful anal lesion, for example, a fissure, it should be employed.

EXAMINATION

Preparation and Position of Patient.—Some proctologists prefer to make the first examination without previous preparation of the bowel. I have found that the difficulty of the examination is greater under such circumstances; there is little to be gained by it and accuracy is impossible. If the examination is to be made in the morning, a purge should be given the evening before, and no supper, or liquids only, permitted. The patient may have breakfast. About an hour before the examination the bowel should be irrigated until the water returns clear. However, the bowel can be quite satisfactorily examined at any time after thorough cleansing enemas have been used.

The knee-chest position is satisfactory for ordinary work. If the patient is weakened by illness or advanced years, the Sims position will probably be more satisfactory. The Haynes proctoscopic table permits the patient to rest in an ideal position, by literally standing him on his head, and is a splendid accessory if it is necessary to use the proctoscope often. This table can also be converted into a regular operating-table.

The proctoscopy should be preceded by a careful digital

examination. Even when the patient is being re-examined and it is not desired to learn anything by the sense of touch, it will be found that the proctoscope can be inserted much more easily if the anal canal has first been dilated slightly and "smoothed out" by the insertion of a finger in a well-lubricated cot.

Figure 26 gives a fairly accurate idea of the relative positions and directions of the lumina of the anus, the first and second

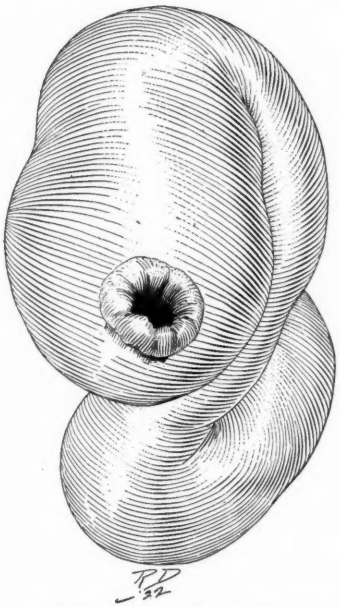

Fig. 26.—The rectum as seen in the knee-chest position.

parts of the rectum, and the pelvic and abdominal sigmoid, with the patient in the knee-chest position. These facts are very important, as will be seen in considering the different maneuvers of passing the proctoscope.

After lubricating the anal canal and the proctoscope thoroughly, the obturator is pressed firmly into the anal orifice (Fig. 27). Many examiners require the patient to bear down at this point, as in the act of defecation, but I find this unneces-

sary; and since it is impossible to pass the scope high in the rectum and into the sigmoid unless the patient relaxes, such a request is often confusing. I therefore encourage relaxation,

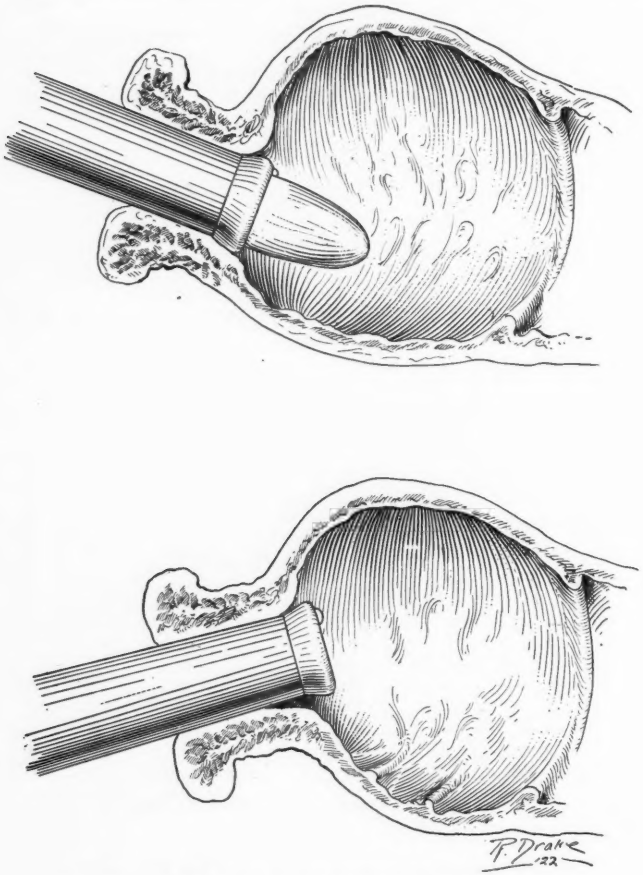

Fig. 27.—The first and second positions of the proctoscope.

as patients strain enough in spite of this. It is necessary to remember the direction of the anal canal, and as may be seen in Figure 27, the instrument is directed slightly anterior to the

horizontal axis of the patient's body. As soon as the anal canal is traversed, the obturator should be withdrawn and all further scoping done under the careful observation of the examiner. When the obturator is withdrawn there is usually an inrush of air so that by merely directing the proctoscope through the lumen of the rectum (pointing it toward the middle point of the sacrum), the bowel may often be explored up to the recto-sigmoid without passing the proctoscope beyond the anus. Great care should be exercised to avoid undue pressure against

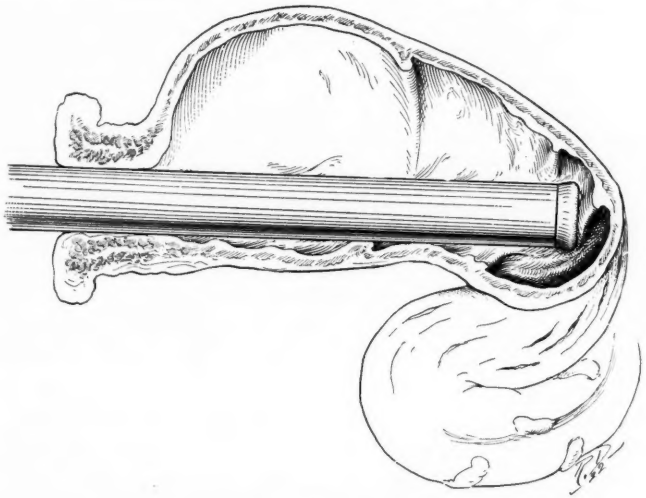

Fig. 28.—The third position in introducing the proctoscope.

the mucous membrane. The sacrum is just beneath the bowel wall posteriorly, and the mucosa may be seriously lacerated as a result of pressure between the metal of the instrument and the bony wall of the sacrum. If this occurs above the peritoneal reflection, serious complications may arise. The scope tip is just opposite the third valve (Fig. 28), and the lower part of the promontory of the sacrum is on the other side of the bowel wall, above the peritoneal reflection. It is, therefore, very necessary to make the next maneuver, as shown in Figure 29.

The anterior wall of the bowel is carefully forced anteriorly until the sacral promontory is out of range, and then for the first time the end of the proctoscope is pressed against the bowel wall. Sometimes resistance is felt even there and if so, no further pressure should be exerted. This interference may be pathologic or due to anatomic irregularity, and added pressure may have serious results. Usually, however, the instrument

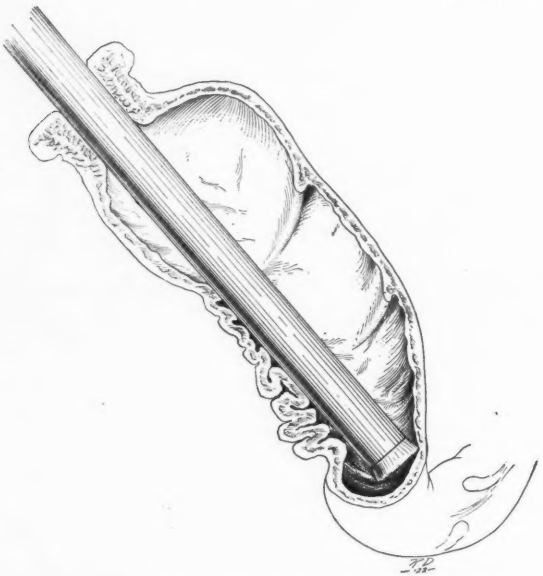

Fig. 29.—The fourth position in introducing the proctoscope.

will slip easily into the sigmoid. It is often necessary first to use the inflator, particularly if the patients are fat or cannot coöperate. As a rule, I do not use air until the prosctocope has been inserted to its full length, and then I use it for two reasons: (1) because in withdrawing the proctoscope the mucosa otherwise clings over the opening in the end in such a way as to make it impossible to see all of the bowel walls, whereas a little air balloons the bowel out and renders the examination much more

thorough and accurate; (2) I am often able to see several inches farther up into the bowel in this manner.

Most of the examination should be made while the scope is being withdrawn. There are, however, exceptions to this rule. In the presence of cancer, no attempt should be made to pass a proctoscope above the lesion unless the lumen is quite free, and the examiner should exercise care to avoid tearing the bowel wall away at the margin of the necrotic mass. Specimens should seldom or never be removed unless operation for removal of the tumor is to be performed immediately, since such irritation stimulates growth. I know of one case which was considered excellent for the radical removal of the growth, in which, two weeks after the taking of a specimen, the growth was fixed in the pelvis and quite inoperable. Cancer of the rectum has a fairly characteristic "feel," but in diagnosis this should not be relied on entirely. However, the appearance of such a growth is unmistakable. Types of ulceration, proctitis, polypi, strictures, and other rectal abnormalities have their characteristics and can be diagnosed by those experienced in the work. For the general practitioner, it is sufficient if he will learn the appearance of a normal rectum, and there are many varieties of the normal. It is not unusual for one who is inexperienced to treat as proctitis a perfectly normal bowel which has nothing more than a pigmented mucosa, and which is not pathologic. If, however, any departure from the normal can be diagnosed, the patient should be referred to the proctologist, who is fitted to make the differential diagnosis, and in this manner prompt and effective treatment attained.

SALIVARY UREA AND THE MERCURY COMBINING POWER OF SALIVA: A NEW AND SIMPLE INDEX OF RENAL INSUFFICIENCY*

PHILIP S. HENCH

ALBUMINURIA, by reason of the ease of its detection, and the general significance of its presence, continues to be the chief criterion on which the diagnosis of renal disease is made. Supplementary data of prime import in the determination of renal insufficiency, however, are the findings of excess metabolites in the blood. The retention of urea, uric acid, and creatinin denotes aberrant renal physiology, and the diminished excretion of foreign substances, such as phenolsulphonephthalein, also indicates insufficiency in renal function by reason of the general parallelism existing between retention of such substances and the waste products of the body.

There is increasing recognition of the fact that the determination of blood urea gives practically all the information of clinical value desired, that might be obtained from the estimations of total nitrogen, non-protein nitrogen, uric acid, and creatinin.[4] The laws controlling the presence and excretion of urea in the body are therefore being subjected to intensive study.

The estimation of the blood urea by the urease method of Marshall, as modified by Van Slyke, although a comparatively simple procedure if certain laboratory facilities are available, is, however, rather complicated and laborious for the use of the general practitioner. Therefore, the phenolsulphonephthalein test of Rowntree and Geraghty remains the most practical and useful means of estimating renal damage quantitatively.

* Work done in the laboratories of the Section on Clinical Investigation, Mayo Clinic.

It has been recognized that urea is easily diffusible, and therefore is approximately equally distributed in all the tissues of the body.[9] Furthermore, all the fluids of the body, including spinal fluid[14] and mammary gland excretion,[1, 10] tend to engage in this equilibration of urea throughout the entire organism. In studying the presence of urea in pleural, pericardial, spinal, and gastric fluids, I have been able to corroborate with respect to these fluids, at least, the general assumption of the existence of such a urea-concentration equilibrium.

Saliva was found to be a very available and useful indicator of urea retention, and in a previous communication[11] Miss Aldrich and I have pointed out the intimate association existing between the concentration of urea nitrogen in the blood, and the concentration of the combined urea and ammonia nitrogen in the saliva. It had previously been noted that urea was present in varying amounts in the saliva of normal persons, and of those suffering with nephritis, but in the analysis of the saliva the presence of differing amounts of ammonia also prevented conclusions as to the relation between the blood urea and the salivary urea.

We found that nearly all of the ammonia in the saliva comes from urea, in the process of the breaking down of urea by oral bacteria in the presence of the alkaline saliva. Therefore, the ammonia should be considered part of the urea, and the combined amount of ammonia nitrogen and urea nitrogen should be considered comparable with the blood urea nitrogen.

In the saliva of normal persons, from 6 to 13 mg. of combined urea and ammonia nitrogen for each 100 c.c. was found, which represents between 13 and 27 mg. of urea for each 100 c.c. Further observations have caused us to consider from 6 to 16 mg. of combined urea and ammonia nitrogen the average range for persons without urea retention, and this combined urea and ammonia nitrogen of the saliva closely approximates that of the urea nitrogen of the blood.

In cases of urea retention, the combined urea and ammonia nitrogen in the saliva always increases with an increase in the blood urea nitrogen, so that in a patient with a blood urea

nitrogen of 218 mg. for each 100 c.c., the saliva contained 158 mg. of combined urea and ammonia nitrogen. Though the combined urea and ammonia nitrogen of the saliva does not always reach the exact amount of the urea nitrogen of the blood the relation of the concentration of the two fluids is very definite, so that the estimation of the combined urea and ammonia nitrogen of the saliva may be regarded as a valuable index of renal functional capacity. The constancy of this relationship depends on the great ease of diffusibility of urea, with the result that urea is present in the saliva incidentally; that is, it is a part of the non-selective secretion of the salivary glands, passing with the specific secretion into the saliva in approximately the same concentration as it reaches the glands by the blood. We have shown that the constancy of the combined urea and ammonia nitrogen in the saliva of a given individual is not appreciably altered by long-continued salivation, or by the action of pilocarpin.

The advantage of estimations of the salivary urea by the urease method, however, is mostly the ease of availability, and the constancy of accessibility of saliva. Blood is not always accessible, especially in children, or in obese patients in whom venipuncture is difficult. An added advantage may be the lowering of the incidence of cubital ecchymoses that are becoming so increasingly numerous as an unavoidable adjunct to studies in blood chemistry. The value of salivary urea determinations has become still greater with the finding of a more rapid and more simple method than the urease method. This consists of the estimation of the mercury-combining power of saliva.

Liebig, in 1853, first developed a titrametric method for the determination of urea in urine. Using mercury nitrate as the reagent, he had considerable difficulty, owing to the presence of large amounts of chlorids in urine. Various other modifications and mathematical corrections were made by Pflüger, Glassmann, and others. Freund and Fellner, in 1902, by using mercuric chlorid, obviated the difficulties resulting from the presence of chlorids. With the advent of other procedures the method was finally discarded.

Friedländer in 1921, also using mercuric chlorid, advocated his modification of Liebig's method for a rapid clinical determination of urea in urine. With this modified Liebig method as a basis we added certain changes of our own, and thereby determined the mercuric chlorid combining power of saliva. In a series of approximately 1000 determinations on the saliva obtained from approximately 500 persons whose blood urea content varied from 12 to 325 mg. for each 100 c.c., we have noted that the mercury combining power of saliva increases with an increase in blood urea and salivary urea, as determined by the urease method.* Therefore, the mercury combining power of saliva may be used as an index of blood urea concentration.

The estimation of the mercury combining power of saliva may be completed in five minutes, using saliva and two easily obtainable reagents. Thus a simple practical method is available whereby an index of the blood urea can be obtained by any practitioner, since it necessitates only the most simple apparatus.

PRINCIPLE UNDERLYING METHOD: DISCUSSION

Bichlorid of mercury in excess in the presence of saturated sodium carbonate gives a reddish-brown precipitate, a mercuric oxychlorid. Not until there is bichlorid of mercury in excess is this precipitate obtained. A deepening canary yellow color is noted before the first brownish-red tinge appears. The saliva has a definite power of combining with varying amounts of bichlorid of mercury. The combination is between bichlorid and certain nitrogenous salivary constituents, mainly urea. On account of the fact that urea represents by far the greater percentage of the combining nitrogenous substances, and because its avidity for bichlorid is much greater than that of the other nitrogenous salivary constituents, the mercury combining power of saliva is an index of the quantitative presence of urea, and the variations in this combining power depend almost entirely on the blood urea concentration. Findings from experiments with standard solutions of urea, uric acid, and so forth, are in accord with the

* Full available chemical and clinical data on this series are about to be published.

data obtained from the saliva in the series of normal persons and patients with urea retention. Saturated bichlorid of mercury was used by Freund and Fellner, and by Friedländer. However, with extreme variations of temperature, the saturation of bichlorid solutions may change approximately from 6 to 7 per cent. Therefore, an error of approximately 15 per cent may be introduced. After utilizing both a saturated and a 5 per cent solution, we have concluded that the use of a 5 per cent solution will exclude this error. The changes in the range of the hydrogen-ion concentration of human saliva are so slight that the necessary chemical reactions are not inhibited.

TECHNIC

Collection of Saliva.—In the previous paper we have discussed in detail the few precautions necessary to avoid contamination of the specimen of saliva. The mouth is first washed out with a half-glass of water. A small piece of paraffin may be used to stimulate salivary flow, and two specimens of about 8 c.c. each are collected. This collection may be made in a very few minutes, and generally without any inconvenience to the patient. The first or preliminary specimen, which removes food particles or excess of epithelial débris, is discarded or may be used as a check on the second specimen, which is used for titration. There may be a slight difference in the combining power of the first and second specimen (usually a very slight increase in the first specimen, 0.1 to 0.3 c.c. for each 5 c.c. saliva). The second specimen is used for titration.

Mercury Titration.—Five cubic centimeters of saliva are measured into a flask by means of a graduated pipet, and titrated with a 5 per cent solution of mercuric chlorid. For the latter, as a rule, a graduated 10 c.c. pipet is sufficient. The addition of bichlorid of mercury is continued until one drop of the mixture, when added to a drop of saturated sodium carbonate on a porcelain plate, causes a definite reddish-brown tinge to appear promptly. Unless the brown color develops within about three seconds, this should not be considered the end point, and a drop or two more of the bichlorid should be

added. The result may be expressed in terms of the cubic centimeters of bichlorid of mercury used to obtain this end point. For the sake of comparative uniformity, however, we have reported our results in terms of cubic centimeters of bichlorid of mercury for each 100 c.c. of saliva. This value we call the "salivary urea index."

It has been found unnecessary to filter the specimens, because we have noted that the epithelial débris has a certain small mercury combining power that practically compensates for the slight quantitative error in the bulk obtained by its presence. Unfiltered, filtered, and supernatant specimens of the same saliva give practically the same result.

DISCUSSION OF RESULTS

For 100 c.c. of saliva the combining power in normal persons is between 30 and 50 (that is, 30 to 50 c.c. of a 5 per cent solution of bichlorid of mercury), or for 5 c.c. of saliva, it is between 1.5 and 2.5 (that is, 1.5 to 2.5 c.c. of a 5 per cent solution of bichlorid of mercury). The upper limit of this range is generally obtained in the presence of the upper limit of normal blood urea concentration which we have taken as 40 mg. for each 100 c.c. of blood. When retention occurs, the mercury combining power rises quantitatively, and at a blood urea concentration of about 325 mg. for each 100 c.c., the mercury combining power is about 270 for each 100 c.c. of saliva, or 13.5 for each 5 c.c. of saliva.

The minute relationship between the mercury combining power of the saliva and the blood urea concentration will not be discussed here in detail. Obviously, by this method closely approximate estimations of the blood urea may be made, utilizing the mercury combining power of saliva.

REPORT OF CASES

A few cases are presented to illustrate the value of the method. In a paper by Drs. Keith and Barrier in this volume, the acute postoperative uremia following nephrectomy is discussed. Data on two of these cases are given herewith.

Case 1 (A413403). Mr. B. D. came to the Clinic December 26, 1922, complaining of bladder trouble. Examination of the urine revealed pus 3

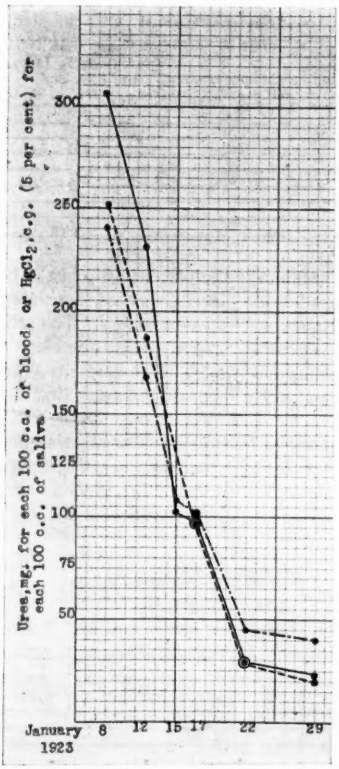

Fig. 30 (Case 1).—Parallel drop in the blood urea, salivary urea, and the salivary urea index (mercury combining power) in a case of postoperative acute retention.

———— denotes salivary urea.
– – – – – – denotes blood urea.
— - — - — denotes salivary urea index.

on a basis of 1 to 4, erythrocytes 1, and positive stain for tuberculosis bacilli. Phenolsulphonephthalein return was 50 per cent. Pyelographic and cystoscopic examination confirmed the diagnosis of renal tuberculosis, and right

nephrectomy was performed December 30th. Acute retention ensued which disappeared under treatment (Table 1).

Table 1
Laboratory data (Case 1)

Date	Blood urea, mg. for each 100 c.c.	Salivary urea, mg. for each 100 c.c.	Salivary urea index, $HgCl_2$ (5 per cent) c.c. for each 100 c.c. saliva	Phenolsulphonephthalein, per cent
1/ 8/23	252	306	240	
1/12/23	187	231	168	
1/15/23		102.9	108	
1/16/23				30
1/17/23	96	97.6	102	
1/22/23	29	29.9	45	
1/24/23				50
1/29/23	20	23.9	40.4	

Figure 30 shows graphically the parallel drop in the blood urea, salivary urea, and "salivary urea index." It will be noted that the salivary urea values were slightly higher than the blood urea values. The salivary urea concentration at high levels is generally slightly below the blood concentration.

In normal persons, and in those with moderate retention, the concentration of urea in blood and saliva more closely approximate each other.

Case 2 (A359894). Mr. L. A. Van H. came to the Clinic January 3, 1923, complaining of backache and hematuria. Examination of the urine revealed albumin 2, erythrocytes 1, pus 1, and was negative for tuberculosis bacilli. Diagnosis of left hypernephroma was made, and a left nephrectomy was performed February 6th. Acute postoperative uremia occurred (Table 2).

Table 2
Laboratory data (Case 2)

Date	Blood urea, mg. for each 100 c.c.	Salivary urea index, $HgCl_2$ (5 per cent), c.c. for each 100 c.c. saliva	Phenolsulphonephthalein, per cent
1/20/23			35
1/26/23	21		
2/15/23		224	
2/17/23	266		
2/19/23	96	73.4	
2/22/23	42	36	

Case 3 (A415958). Mrs. H. C. came to the Clinic January 1, 1923, and a diagnosis of bilateral pyelonephritis was made. Examination of the urine revealed pus 3 and 4, albumin 2, and erythrocytes 1. The blood urea was 20 mg. The temperature and pulse were normal. The patient was dismissed, but returned to the Clinic March 23. At this time blood urea could not be obtained. The salivary urea index was determined April 8th. Two days later the patient developed high temperature and rapid pulse, with headache and nausea. This case illustrates the possibility of studying urea retention when blood urea estimations are impossible (Table 3).

Case 4 (A472479). Mr. P. O., aged sixty-five years, had acute and chronic retention, and was observed over a considerable period of time. The

Table 3
Laboratory data (Case 3)*

Date	Salivary urea, mg. for each 100 c.c.	Salivary urea index, $HgCl_2$ (5 per cent), c.c. for each 100 c.c. saliva	Clinical notes
4/ 8/23		54	Temperature and pulse normal
4/10/23			Temperature 103; pulse 135
4/11/23			Temperature 103; pulse 130
4/12/23	70.5	71.4	Temperature 99.5 to 102.5; pulse 112 to 102
4/14/23			Temperature and pulse normal
4/17/23		54	
4/19/23	34	32	

*This case illustrates the possibility of studying urea retention where blood urea estimations are impossible.

Table 4
Laboratory data (Case 4)

Date	Blood urea, mg. for each 100 c.c.	Salivary urea index, $HgCl_2$ (5 per cent), c.c. for each 100 c.c. saliva	Phenolsulphonephthalein, per cent	Clinical notes
12/13/22	226	192		Venesection 750 c.c.; transfusion 500 c.c.
12/14/22			No return	
12/16/22 to 2/17/23			5-10-15	Four transfusions
2/18/23	100	90	10	Improving
2/20/23	112	108		
2/24/23	96	90		
2/27/23	80	78		
3/ 2/23			15	
3/ 3/23	64	72		
3/ 7/23	66	66		
3/ 9/23	56	60		
3/10/23		54		
3/16/23	52	57	15	
3/20/23	60	66		
3/23/23	62	60		
3/27/23	68	60		
3/30/23	60	66		

bladder was gradually decompressed. A diagnosis of hypertrophied prostate, 2, with uremia was made (Table 4).

Comparisons between the blood urea, salivary urea, and the mercury combining power of saliva were made in approximately 500 cases. The findings in certain selected cases are given in Table 5.

From these examples the value of the method to obtain a rapid idea as to the absence or presence, and approximate degree of retention, will be seen. Cases in hospitals may be followed

Table 5

Comparison of blood urea, salivary urea, and mercury combining power of saliva*

Blood urea, mg. for each 100 c.c.	Salivary urea, mg. for each 100 c.c.	Salivary urea index, $HgCl_2$ (5 per cent), c.c. for each 100 c.c. saliva
24	22.8	39
30	25	42
31	29.1	45
44	35.7	51
53	48.1	58.4
91	74	81
158	117	100
228	220.4	171
264	248.2	222

*Findings selected from a series of approximately 500 cases

daily with occasional checks on the blood urea. The method may be used routinely before blood urea estimations are made, and thus the inconvenience of unnecessary venipunctures avoided. When blood urea estimations are impossible, it may be used as a useful adjunct to urinalysis and the phenolsulphonephthalein test, since the specimens may be collected at the bedside and analyzed in the physician's office. The method may be used as an office test for detecting cases of retention. We have on several occasions detected definite unsuspected urea retention in ambulatory cases, and have sent them at once to the hospital where later blood urea estimations have confirmed the indications of the salivary urea index.

SUMMARY

The concentration of urea in the saliva increases in approximately the same relationship as the blood urea concentration, although slightly lower figures are generally obtained.

A study was made of the mercury combining power (5 per cent bichlorid of mercury) of saliva in normal persons and in patients with urea retention. It was observed that there was a direct parallelism between the estimations of the mercury combining power of saliva and the estimations of blood urea.

A simple test is presented to determine the mercury combining power of saliva, which will indicate the degree of blood urea

retention. This is expressed in cubic centimeters (5 per cent bichlorid of mercury for each 100 c.c. saliva), which we call the salivary urea index. Its use is advocated as a routine procedure in the study of renal function, as an adjunct to the phenolsulphonephthalein test, and in place of estimations of blood urea in cases in which such estimations would be of necessity frequent, or, especially if they are not obtainable because of lack of proper laboratory facilities. The values will not always agree absolutely, but will run parallel.

CONCLUSIONS

1. The combined urea and ammonia nitrogen of saliva of normal persons is approximately from 6 to 16 mg. for each 100 c.c., representing from 13 to 33 mg. urea for each 100 c.c. saliva.

2. In urea retention the combined urea and ammonia nitrogen of saliva is increased in definite relationship to the increase of blood urea nitrogen.

3. The mercury combining power of saliva normally varies between 30 and 50 (c.c. bichlorid of mercury) for each 100 c.c. saliva.

4. The mercury combining power of saliva increases with urea retention.

5. The mercury combining power of saliva may be utilized as a urea index.

BIBLIOGRAPHY

1. Denis, W., Talbot, F. B., and Minot, A. S.: Non-protein nitrogenous constituents of human milk. Jour. Biol. Chem., 1919, xxxix, 47–51.
2. Freund, E., and Fellner, R.: Ueber Bestimmung der stickstoffhaltigen Urinbestandtheile mit Sublimat. Hoppe-Seyler's Ztschr. f. physiol. Chem., 1902, xxxvi, 401–406.
3. Friedländer, E.: Titration des Harnstoffes im Urin für klinische Zwecke. München. med. Wchnschr., 1921, lxviii, 1225–1226.
4. Frontz, W. A., and Geraghty, J. T.: The value of the estimation of urea, nonprotein, nitrogen and creatinin as an index of renal function. Jour. Am. Med. Assn., 1922, lxxix, 1383–1384.
5. Glassmann, B.: Zur quantitativen Bestimmung des Harnstoffs. Ber. d. deutsch. chem. Gesellsch., 1906, xxxix, 1, 705–710.
6. Hench, P. S., and Aldrich, Martha: The concentration of urea in saliva. Jour. Am. Med. Assn., 1922, lxxix, 1409–1412.

7. Liebig, J. v.: Ueber einige Harnstoffverbindungen und eine neue Methode zur Bestimmung von Kochsalz und Harnstoff im Harn. Ann. d. Chem., 1853, lxxxv, 289–328.
8. Marshall, E. K., Jr.: A new method for the determination of urea in blood. Jour. Biol. Chem., 1913, xv, 487–494.
9. Marshall, E. K., Jr., and Davis, D. M.: Urea: Its distribution in and elimination from the body. Jour. Biol. Chem., 1914, xviii, 53–80.
10. Myers, V. C., and Fine, M. S.: Comparative distribution of urea, creatinin, uric acid, and sugar in the blood and spinal fluid. Jour. Biol. Chem., 1919, xxxvii, 239–244.
11. Pflüger, E.: Ueber die quantitative Bestimmung des Harnstoffs. Arch. f. Physiol., 1880, xxi, 248–286.
12. Pflüger, E.: Kritische und experimentelle Beiträge zur Titration des Harnstoffes. Arch. f. Physiol., 1880, xxiii, 127–150.
13. Rowntree, L. G., and Geraghty, J. T.: The phthalein test. An experimental and clinical study of phenolsulphonephthalein in relation to renal function in health and disease. Arch. Int. Med., 1912, ix, 284–338.
14. Taylor, W.: Note on the non-protein nitrogen in goat's milk. Biochem. Jour., 1922, xvi, 611–612.
15. Van Slyke, D. D., and Cullen, G. E.: A permanent preparation of urease and its use in the determination of urea. Jour. Biol. Chem., 1914, xix, 211–228.

ACUTE RENAL INSUFFICIENCY FOLLOWING MAJOR SURGICAL OPERATIONS

CHARLES W. BARRIER
AND
NORMAN M. KEITH

IT is recognized that oliguria or anuria occurs in acute or chronic renal lesions, and that in many instances patients recover. Numerous cases of acute nephrosis due to bichlorid of mercury poisoning have been reported, and in spite of anuria and other very alarming symptoms, the patients recover satisfactorily. Patterson and Lambert, Lewis and Rivers, and others have studied many such cases in detail. Keith and Thomson have reported recovery from oliguria in cases of acute glomerular nephritis. Severe renal insufficiency followed by satisfactory recovery has been noted by Brown, Eusterman, Hartman, and Rowntree in several cases of high intestinal obstruction. Hardt and Rivers report the occurrence of impaired renal function, as shown by retention of urea and creatinin in patients with duodenal ulcer while on the Sippy alkali régime. In some of these, normal renal function returned under proper management. Likewise there are many cases of nephrectomy reported in which, even though the opposite kidney functioned adequately before operation, anuria and retention of nitrogenous substances in the blood occurred after operation. McCarthy, Killian, and Chace have recently reported a case of so-called reflex anuria and oliguria of long duration with a high retention of urea nitrogen and creatinin, and with symptoms of uremia followed by recovery. Four cases are herewith reported in which, following major surgical operations, there was anuria or oliguria of short duration with greatly increased blood urea and creatinin, but without characteristic symptoms of uremia. In all there was a satisfactory return of renal function. Cases of prostatic enlargement

with bladder retention and renal back pressure, in which severe renal insufficiency is indicated by increased amounts of blood urea and creatinin, are common. Restoration of renal function often follows surgical removal of the prostate.

REPORT OF CASES

Case 1 (A413403). A single man, aged twenty-two years, came to the Clinic December 12, 1922, complaining of frequency and hematuria. He had had influenza in 1918, and quinsy, followed by tonsillectomy, in 1920. In July, 1922 he had had pain in the lower part of the back, and occasional mild burning on urination. The pain in the back soon disappeared, but the burning sensation increased; marked frequency, both day and night, developed, and the urine became blood-streaked with terminal clots. The patient had had considerable pyuria, but no fever, chills, or passing of calculi. He had lost twelve pounds in weight.

At examination there was tenderness in the region of the right kidney; the caliber of the retinal arteries was somewhat reduced; the blood-pressure was 134 systolic, and 100 diastolic; the pulse was 80, with numerous extrasystoles, and the temperature was 99.3° F. A roentgenogram of the chest revealed a thickened pleura at the right base, and a healed tuberculous lesion at the right apex. The urinary output for twelve hours was 750 c.c.; specific gravity was 1010; urinalysis revealed albumin 2, sugar 0, erythrocytes 1, and pus 3, and tuberculosis bacilli were present. The phenolsulphonephthalein return was 50 per cent when given intramuscularly; the blood count was hemoglobin 87 per cent, leukocytes 9800. The Wassermann reaction was negative, and the roentgenogram of the kidney, ureter, and bladder was negative. The cystoscopic examination revealed a functionless right kidney with tuberculosis bacilli. The left kidney was free from tuberculosis bacilli, as shown by stains from the left ureter and guinea-pig inoculations.

The right kidney was removed December 30, 1922, and pathologic examination revealed a tuberculous lesion with destruction of one-third of the kidney substance. Urine was not passed, except by catheter, until the fifth day, and then in small amounts (Table 1). During the period of suppression, the patient received coffee, lemonade, and a 10 per cent solution of glucose, intravenously; fluids were forced by mouth and rectum, and he was kept on a low protein diet. January 11, 1923 he was transferred to the medical service, and put on a salt-free diet of 3000 calories, containing 20 gm. of protein. Five pints of fluid were also given. On the seventeenth day after operation, although the patient was given 1500 c.c. of water between 8:00 and 8:30 a.m., his urinary output was only 500 c.c. in four hours, and the specific gravity was never less than 1008. On the thirtieth day, on the same régime, he voided 793 c.c. in four hours, the urine being as dilute as 1002. The highest specific gravity reached on the nineteenth day, while on a water fast for thirty-six hours, was 1015, and on the thirty-first day, on the same régime, 1016.

Clinically, the patient did not appear very ill during the period of exces-

sive blood urea, and after the urea began to diminish he was given a high calorie diet, and gained in weight and strength. The only complaint was frequency, resulting from tuberculous involvement of the bladder and prostate.

TABLE 1

			Blood findings				Urine findings							
	Temperature	Blood pressure	Hemoglobin, per cent	Urea, mg. in each 100 c.c.	Creatinin, mg. in each 100 c.c.	Carbon dioxid combining power, volume, per cent	Twenty-four hour specimen, c.c.	Specific gravity	Albumin	Casts	Red blood cells	Leukocytes	Phenolsulphonephthalein, per cent	Remarks
Case A413403														
Preoperative	99.6	134/100	87				750	1010	2	0	1	3	50	
Postoperative, first day	98.0						0	1007						No vomiting Fluids forced
Second day	101.0						100							
Fourth day	101.5	*		212	12.0		210							
Fifth day	98.6						640		2		1	2		
Sixth day	98.6			274	13.5		1250							
Tenth day	98.6			252	12.0									
Fourteenth day	98.6			187	6.4	59.0	1900	1010	1		1	2	30	
Twenty-second day	98.6	†	90P	29	2.2		2500	1005	1		1	1	50	
Case A359894														
Preoperative	98.6	166/120	78	28			1750	1019	2	0	1	1	70	
Postoperative, first day	98.6						0							No vomiting Fluids forced
Second day	101.0						60							
Fifth day	98.6			242	12.4		420							
Sixth day	98.6						1220							
Twelfth day	98.6			212	12.8									
Fourteenth day	98.6												35	
Seventeenth day	98.6			42			1300	1005	1	1	1	1		
Twenty-first day	98.6		87P	21	1.3									
Case A385334														
Preoperative	100.0	112/80	69				1350	1015	3	0	1	3	70	
Postoperative, first day	98.0						90							No vomiting Fluids forced
Fourth day	103.0		69	190		50.4	30							
Sixth day	99.0						105							
Eighth day	98.6			378	10.3		600	1009	2		1	3		
Tenth day	98.6	130/94		400	7.5								5	
Thirteenth day	98.6		68	382	7.2		2080							
Twenty-sixth day	101.0			136	2.0									
Thirty-third day	98.6			18										
Eleven months later			76	34									50	

* Third day blood-pressure 146/96.
† Eighteenth day blood-pressure 115/80.

Case 2 (A359894). A married man, aged thirty-eight years, was examined at the Clinic June 1, 1921. He had had backache for eight years. Seven years before he had had his gallbladder and appendix removed. Two years before, he had had influenza, and six weeks before pneumonia. He was subject to attacks of grip. In 1920 he had had one attack of hematuria, with slight pain over the region of the kidney. He complained of soreness in the muscles of the neck, shoulders, and back, nasal trouble, and dyspnea on exertion. Examination revealed septic tonsils and teeth, which were removed. The urinalysis was negative, and the patient was therefore dismissed, with instructions to return if there was a recurrence of hematuria.

The patient returned to the Clinic January 1, 1923. He had had hema-

turia for nine months, and in November, 1922 the attack was accompanied by lumbar pains so severe as to require morphin. He complained of frequency, and of scanty urination following hematuria.

At examination a large tumor was found in the left side. The blood-pressure was 166 systolic and 120 diastolic. Urinalysis revealed albumin 2, and erythrocytes and leukocytes 1; the blood urea was 28; the blood count was normal, and the return of phenolsulphonephthalein given intravenously was 70 per cent. The heart was enlarged 1. A diagnosis of hypernephroma was made, and operation advised.

February 2d, at operation, a large hypernephroma was found destroying almost the entire substance of the kidney, and involving the perirenal fat and neighboring lymph-glands. A left nephrectomy was performed. The patient passed no urine on the first day, 60 c.c. of bloody urine by catheter on the second day, 65 c.c. on the third day, 440 c.c. on the fourth day, 420 c.c. on the fifth day, and 1220 c.c. on the sixth day (Table 1). He was somewhat drowsy, but showed no signs of uremia, and eventually made a satisfactory recovery with return of good renal function.

Case 3 (A385334). A single man, aged twenty-five years, came to the Clinic March 2, 1922, complaining of hematuria, pyuria, and frequency. In 1917, while in the army, he had had influenza, and pneumonia twice. He had not been well since, and had developed night-sweats, soreness of chest, cough, and a tendency to sore throat and hoarseness. In November, 1921 burning on urination, frequency, hematuria, and pyuria had developed. He had lost 28 pounds in three years.

On examination he was found to be running a low-grade temperature. There were signs of consolidation at the base of the right lung, and the prostate was enlarged and tender. Urinalysis revealed albumin 3, pus 4, and tuberculosis bacilli. The phenolsulphonephthalein output was 70 per cent in two hours. Cystoscopic examination revealed a tuberculous, functionless right kidney; the urine from the left was free from tuberculosis bacilli, and the kidney had excellent function. There was a reaction following the cystoscopic examination, and the patient developed a cold which delayed the operation until April 5th, when a right nephrectomy was performed. Pathologic examination of the removed kidney revealed a tuberculous lesion with multiple abscesses, and destruction of about 60 per cent of the kidney substance. Following operation the patient developed anuria (Table 1), appeared dull mentally, but was not alarmingly ill. Recovery was satisfactory, with a return of good kidney function.

Case 4 (A360199). A married man, aged forty-six years, came to the Clinic June 6, 1921. He had had pain and soreness in the epigastrium for twenty-five years, which had been worse during the last five years. It was intermittent, and came on two or three hours after meals, and at night. Relief was obtained by taking food and soda, by induced vomiting, by drinking, or by using the hot-water bottle. By remaining on a diet the patient was able to obtain more or less continued relief.

At examination the patient's weight was 153 pounds; the blood-pressure was 135 systolic, and 75 diastolic; the phenolsulphonephthalein return was 65 per cent; urinalysis and the Wassermann reaction were negative. Gastric

analysis revealed total acid 66, free hydrochloric acid 55, and fluid 175 c.c. A roentgenogram of the stomach revealed a perforated ulcer of the lower curvature, with retention 3. Medical treatment was given for four days before operation.

At operation, June 13, 1921, a large perforating gastric ulcer was found, and a partial gastrectomy with end-to-side anastomosis was performed. Three or four hours later 500 c.c. of citrated blood was transfused. The patient vomited a pint of blood during the night, and for the next few days gastric lavage revealed blood mixed with bile in quantities as high as 500 c.c. On the fourth day the patient took water freely by mouth. The urinary output the first day after operation was nil; the second day, 180 c.c.; the third day, 300 c.c.; the fourth day, 390 c.c.; the fifth day, 2100 c.c., and the sixth day, 1140 c.c. On the third day after operation the blood urea was 298, creatinin 5, plasma carbon dioxid combining power 52 volumes per cent, pulse 84 and regular, and respiration 20. The blood-pressure was 115 systolic, and 65 diastolic. The temperature ranged from 100 on June 14th to 102.4, June 16th. The patient seemed drowsy, but was mentally clear. There was no edema, and the eye-grounds were negative. June 18th, the blood urea was 328, and the creatinin 4.4. June 29th, the patient was transferred to a convalescent hospital. July 1st the blood urea was 53 mg., and the creatinin, 1.6. July 3d he had a severe gastric hemorrhage, and a transfusion of 725 c.c. of citrated blood was given; the next day a second transfusion of 500 c.c. was given. July 11th a single voiding of urine amounted to 1000 c.c.; in this albumin 0, and pus 4 were noted. July 15th the blood urea was 38 mg., and the creatinin 1.7. Recovery was satisfactory.

DISCUSSION

Nephrectomy was performed on three patients and partial gastrectomy on one. The three patients did not vomit, the fourth vomited, probably because of a local gastric condition. All of the patients had had satisfactory renal function before operation. In the three patients on whom nephrectomy was performed, cystoscopic examination had shown that the diseased kidney was practically without function, while the other functioned adequately.

Immediately after operation oliguria or anuria developed. Later there was a rapid rise in the nitrogenous bodies in the blood. The amount of nitrogen, as indicated by urea and creatinin in the blood, reached its maximum in from one to two weeks; the blood urea became normal within three to four weeks after onset. Our findings, although not complete, would indicate that the retention of nitrogen persisted for a short time after the total output of urine had become normal.

It is of interest to note the occurrence of a blood urea of 400 mg. and creatinin of 13.5 mg. in 100 c.c., with so few clinical symptoms of toxemia. As we have mentioned, vomiting was not a feature of these cases. Except for a slight drowsiness, consciousness was unaltered, and there were no headaches. At no time was respiration distinctly abnormal. The absence of muscular twitchings, or of any convulsive phenomenon was striking. Edema was never demonstrable. In fact, nothing on physical examination, or in the patient's clinical condition, suggested the existence of a serious toxemia.

The therapeutic measures employed were a low protein and low salt diet, and ingestion of 2500 to 3000 c.c. of fluid daily. Some of the patients were given strong coffee repeatedly by mouth or rectum; one patient was injected intravenously with a 10 per cent glucose solution.

Our findings emphasize the fact that severe acute renal insufficiency can occur with subsequent apparent recovery. Even extremely marked retention of urea and creatinin should not deter the carrying out of indicated therapeutic measures. In spite of these very abnormal findings in the blood the prognosis is not necessarily grave.

BIBLIOGRAPHY

1. Brown, G. E., Eusterman, G. B., Hartman, H. R., and Rowntree, L. G.: Toxic nephritis in pyloric and duodenal obstruction: Renal insufficiency complicating gastric tetany. Arch. Int. Med. (In press.)
2. Hardt, L. L. J., and Rivers, A. B.: Toxic manifestations following the alkaline treatment of peptic ulcer. Arch. Int. Med., 1923, xxxi, 171–180.
3. Keith, N. M., and Thomson, W. W. D.: War nephritis. A clinical, functional, and pathological study. Quart. Jour. Med., 1917–1918, xi, 229–266.
4. Lambert, S. W., and Patterson, H. S.: Poisoning by mercuric chlorid and its treatment. Arch. Int. Med., 1915, xvi, 865–879.
5. Lewis, D. S., and Rivers, T. M.: Chemical studies on a case of bichloride poisoning. Bull. Johns Hopkins Hosp., 1916, xxvii, 193–201.
6. McCarthy, J. F., Killian, J. A., and Chace, A. F.: Reflex anuria. Report of a case with unique blood chemistry findings and an unusual application of the duodenal tube. Jour. Am. Med. Assn., 1923, lxxx, 1043–1047.

REPORT OF A CASE OF DUPLICATION OF THE RENAL PELVIS AND URETER, WITH EXTRAVESICAL OPENING OF ONE URETER RESULTING IN HYDRONEPHROSIS OF THE UPPER PELVIS AND HYDRO-URETER

HERMON C. BUMPUS, JR.

Case A313852, a man, aged forty-seven years, came to the Clinic for treatment of his right femur, which had been fractured in an accident a number of months before. Four attempts by surgical procedures had been made to obtain union, without satisfactory results, and the patient, besides being unable to use his leg, had a discharging sinus.

The general examination was negative except that the urine contained a large amount of pus. Roentgenograms of the right femur revealed forward displacement and faulty union. The patient was transferred to the orthopedic section for treatment, and during convalescence following surgical procedures on his femur he had an acute attack of severe general abdominal pain which later localized to the right side. The pain, which at times radiated to the right testicle, was associated with nausea and vomiting, and a temperature of 101°. The soreness persisted for several days, but gradually subsided. A mass could not be palpated. The patient said that he had been subject all his life to similar attacks, usually lasting from three days to a week and often associated with colic sufficiently severe to require morphin. Immediately after the attacks he had noticed a desire to urinate more frequently, and sometimes suffered from slight dysuria, when the urine seemed to be more cloudy than usual. Because the patient seemed to have recovered following his last attack, no investigation was made of its cause and all therapeutic measures were directed toward the condition of the femur. After the patient was dismissed from the hospital he obtained employment in the city, and after a lapse of several months again came to the Clinic because of an asthmatic attack from which he had not fully recovered. He said that these attacks also were periodic and had existed the greater part of his life, but that usually he recovered quickly. He had never noticed any seasonal relationship.

While the patient was being observed in an endeavor to locate a possible focus of infection to account for the asthma, and sensitization tests were being made, he developed an attack of colic similar to the one described. The physician who saw him in the attack felt confident that it was of renal origin, and the presence of large amounts of pus in the urine seemed to confirm this belief. Roentgen-ray examinations, however, failed to reveal shadows

suggestive of calculi, and cystoscopic examination revealed a normal bladder free from cystitis. Urine from both ureters did not contain pus. A pyelogram (Fig. 31) was made of the right kidney, but aside from the fact that the organ was located at a distance from the spine its condition was not considered remarkable, although the possibility that a cyst of the upper pole caused the abnormal position was considered. Several weeks afterward the patient had a second attack of colic still more severe, and on being questioned said that immediately after the cystoscopic examination he had passed large quantities of almost pure pus. This fact, together with the lateral dis-

Fig. 31 (Case A313852).—Pyelogram of lower pelvis giving the impression of a normal single kidney. Note the lateral displacement which is the only suggestion of a possible duplication.

placement of the renal pelvis, suggested that the patient must have an extravesical opening of a duplicate ureter, the upper pelvis causing by its size the lateral displacement of the lower pelvis, which was otherwise normal and uninfected. Because the upper pelvis always opens to the inner side and below the orifice of the lower pelvis, search for it was first made in the bladder, indigocarmin having first been given intravenously. The orifice not being found there, the prostatic urethra was next examined, and in the floor in the musculature of the internal sphincter the opening was found, a spurt of cloudy urine having first been noted. The patient was catheterized through this orifice and a pyelogram made (Fig. 32). The size of the hydronephrosis and

hydro-ureter was so great that although a large amount of 12 per cent solution of sodium iodid (45 c.c.) was injected, the pyelogram was poor. However, it was sufficiently distinct for purposes of diagnosis, and showed the dilated ureter, equal in size to the large intestine, pursuing a tortuous course to a huge hydronephrosis of the upper pole of the double kidney. The function of the upper pelvis was so largely destroyed that no indigocarmin or phenol-sulphonephthalein was excreted.

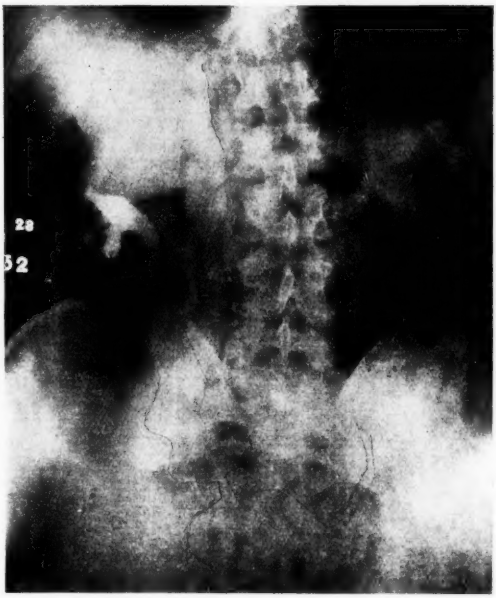

Fig. 32 (Case A313852).—Pyelogram of lower pelvis and upper pelvis and ureter. The upper pelvis has become a hydronephrotic sac with a greatly dilated ureter. The dilatation being so great the iodid is diluted and the picture has been retouched to show the course of the ureter.

This case has certain points of individual interest besides the general points connected with the anomalous condition. It seems possible that the delayed healing and the persisting sinus after so many operations on the fractured femur might well have been due to the large focus of infection, or at least that this so impaired his general health that normal healing was

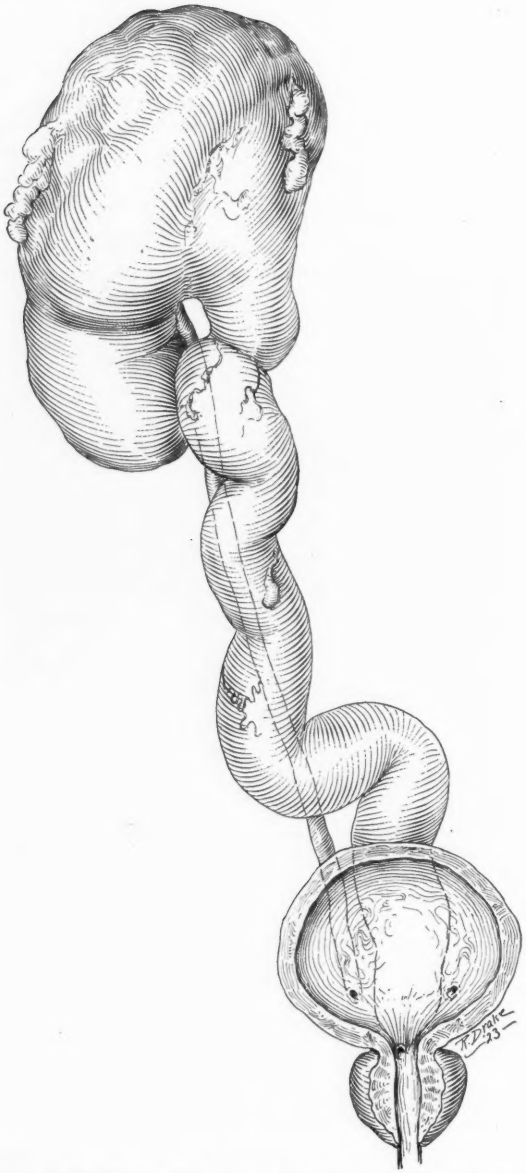

Fig. 33.—Double kidney with hydronephrotic upper pelvis and ureter. Note the insertion of the hydronephrotic ureter in the bladder sphincter.

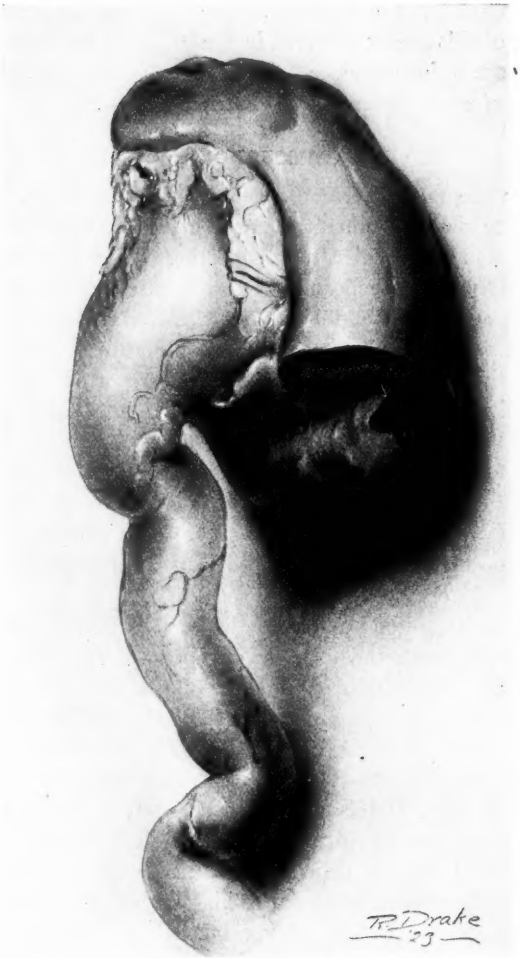

Fig. 34.—Specimen consisting of upper hydronephrotic pelvis and ureter removed at operation.

prevented. Also, the frequent attacks of asthma occurring without relationship to the seasons might well be explained by

this constant focus of infection. The fact that the extravesical opening of this ureter occurred in the prostatic urethra explains the absence of incontinence, which is usually the chief symptom in cases of extra ureters having extravesical openings.

DISCUSSION

Since urography became a general procedure, the common occurrence of double ureters and renal pelves has been recognized. Braasch and Scholl, at a recent meeting of the American Urological Association, reported 144 such cases, observed in the Clinic between 1907 and 1922, and C. M. Harpster and others reported 382 cases collected from the literature. In these two groups the supernumerary ureter was reported as opening extravesically in thirty-three cases. At the same meeting Furniss reported two cases of extravesical openings, and said that up to that time fifty-one cases, including his own, had been reported. It is evident, therefore, that although the extravesical opening of a supernumerary ureter is relatively uncommon, it occurs sufficiently often to make its recognition important.

In order to search intelligently for such extravesical openings, a familiarity with the fetal development of the structures is important. In embryonic life the wolffian duct gives off the bud which is to form the ureter, renal pelvis, and, in fact, all the collecting portion of the kidney. As this bud elongates in its growth upward, it sometimes splits so that two ureters develop in place of one. If this splitting occurs late in development, a double pelvis results with individual ureters uniting near the kidney or far from it, depending on the period in development at which the change occurred. This division sometimes occurs simultaneously with the giving off of the kidney bud, or two separate buds occur, resulting in two openings into the wolffian duct. If development progresses normally, the two openings will ultimately become ureteral orifices in an otherwise normal bladder. The lower or mesial orifice in adults is always connected with the higher renal pelvis. This is owing to the fact that during the development of the ureters the wolffian duct

turns and travels down to lodge permanently at the neck of the bladder, and in so doing pulls the upper ureter with it in its descent, which results in a reversal of the original relationship of the two ureteral orifices. This change of position explains the fact that double ureters always cross at some point.

If, as the bladder and urethra develop from the allantois, the opening of the lower ureter is pulled too far down by the wolffian duct, which now forms the seminal vesicles and ejaculatory ducts in the male, it may, instead of opening into the bladder, open into the urethra or be carried into the seminal vesicles. In the female, failure of the ureter to open near its companion in the bladder, and the appearance of the orifice anywhere in the genital tract from the urethra to the fallopian tubes, is explained by the same process.

One would expect, then, to find the greatest number of ectopic openings near the neck of the bladder in the urethra and the fewest further out along the genital tract, either in the fallopian tubes or seminal vesicles. In the thirty-three cases reported in which the location of the extravesical orifice is given, seventeen opened at some point along the urethra, six into the vulva, usually just below and very close to the external urethral meatus, six into the vagina, always at some point on the anterior wall and usually in close proximity to the urethra, and one into the seminal vesicles. In three cases, although the vesical opening was absolutely excluded, the extravesical opening could not be located.

When the double ureters both open into the bladder, the incidence of disease in one or the other renal pelvis, or both pelves, will be high, for an abnormal organ is more susceptible to disease than the normal one. In 58 per cent of the 144 cases observed in the Clinic, definite pathologic conditions were present, and in thirty patients surgical interference was required.

When one of the ureters opens outside of the bladder, evidence of disease is markedly increased; certain observers assert that lesions are continually found in the part of the kidney corresponding to the abnormal opening. Infection, hydronephrosis and hydro-ureter are the most common findings

because the majority of the ectopic openings occur in the urethra, and the ureter can only discharge its contents during the act of micturition. This produces, as in the case reported, a perpetual intermittent obstruction which affords ideal conditions for the formation of a greatly enlarged ureter and pelvis, while it permits just sufficient escape of urine to prevent complete destruction of the secreting tissue of the kidney.

Symptoms.—These naturally vary with the location of the ectopic opening. If it is in the urethra on the vesical side of the external sphincter, there will be no incontinence, although frequency and dysuria may be marked, especially if secondary infection has produced posterior urethritis. The pain and colic resulting from complete ureteral obstruction, that occurred at intervals of several years in the case reported here, was the most marked symptom. The attacks in every way simulated the renal colic resulting from the passage of a calculus, although the roentgenographic findings were negative. The number of patients who suffer from such attacks of unexplained colic is fairly large, and undoubtedly includes certain patients with extravesical openings of duplicate ureters. Such symptoms are often attributed to ureteral strictures, although the presence of such strictures is not demonstrable.

The passage of large amounts of purulent urine after normal appearing urine had been voided was a symptom at once suggesting diverticulum either of the bladder or the urethra. With diverticulum of the urethra there is usually a history of the patient having forced out the purulent terminal urine by manual pressure on the perineum. Diverticulum of the bladder is readily detected by a cystogram.

Heavily infected urine, in the absence of cystitis or renal infection, always centers attention on the prostate as the source of the infection, and an ectopic orifice may readily be mistaken for a dilated prostatic duct, but such dilated ducts are always multiple. This finding, however, is generally of little aid, as the opening of a supernumerary ureter into the prostatic urethra causes sufficient inflammation to dilate all the ducts. Therefore, when proper treatment of the prostate has not seemed to

diminish a marked urinary infection that is not confined to the bladder or ureters, suspicion of an ectopic orifice must be entertained. If this persistent unexplained pyuria is associated with symptoms of renal colic, as in the case reported, then suspicion of an undetected ureteral orifice must be entertained. When the opening is outside of the sphincters, the history is that of constant incontinence since birth, associated with normal voiding. This condition should always instigate search for an ectopic ureteral orifice.

Diagnosis.—In the diagnosis of duplication of the renal pelvis and ureter, the intravenous injection of indigocarmin, or the oral administration of methylene-blue, will often be of the greatest service provided one is not misled by the finding of two normal ureters spurting normally. Usually the third ureter will excrete sufficient methylene-blue to mark the location of the opening. If it is not found readily, packing of the vagina and vulva with cotton will sometimes result, after several hours, in a telltale spot of blue on the packing.

If the renal function is reduced sufficiently to prevent adequate secretion of the dye, or if the hydronephrosis and hydroureter are great, the diagnosis will depend largely on the pyelographic findings. If a pyelogram has been made of one pelvis of a double kidney, the deformity shown is very likely to be misinterpreted, especially if there are other evidences of renal disease. Thus, when but one ureteral orifice is found and the pyelogram shows a markedly shrunken renal pelvis with retracted calices, and the renal function is poor, it is natural to assume that one is dealing with a case of atrophic pyelonephritis. The kidney, as a result of long-continued infection having become largely fibrotic, retains but little of its secreting outline. If there is a history of pain and the double kidney is felt as a mass, the finding of a small and distorted pelvis may suggest neoplasm. These errors in diagnosis most often occur when the upper of the two pelves is injected, for the upper pelvis is usually much smaller than the lower and much more deformed, but being closer to the normal position of the kidney than the lower pelvis it is not as likely to suggest the presence of a second pelvis.

When the ureters are joined in their course from the bladder, this pitfall is not so likely to be present, as the pyelographic medium usually runs back along the ureter that has been injected and up the other ureter, thus revealing the duplication. If the ureters are separate throughout their entire course, the condition, of course, will not be revealed by pyelography, and if the extra orifice in the bladder is not noted, or if it is extravesical, the condition may pass unrecognized. When the lower of the two pelves is injected, as was done in the case reported, there is usually marked indication of a double kidney. Either the upper calyx will be entirely absent, suggesting that a tumor or second pelvis has obliterated it, or, as occurred here (Fig. 32), the pelvis, although comparatively normal, is situated so far from the spine as to suggest the presence of a second pelvis above. In this case the displacement was extreme, owing to the size of the hydronephrosis.

Summary.—This type of case is probably more common than is recognized, since finding it in adults indicates the lack of appreciation of its existence. The presence of unexplained, apparent, renal colic in a patient with negative urologic findings should suggest a double ureter, and the occurrence of marked pyuria under similar conditions should suggest like findings.

BIBLIOGRAPHY

1. Braasch, W. F., and Scholl, A. J., Jr.: Pathologic complications with duplication of the renal pelvis and ureter. Jour. Urol., 1922, viii, 507–558.
2. Bumpus, H. C.: Diverticula of the posterior urethra. Surg., Gynec., and Obst., 1919, xxix, 388–392.
3. Furniss, H. D.: Supernumerary ureters with extravesical openings. Jour. Urol., 1922, viii, 495–505.
4. Harpster, C. M., Brown, T. H., and Delcher, H. A.: Abnormalities of the kidney and ureter. Jour. Urol., 1922, viii, 459–490.

SOME ASPECTS OF ENURESIS IN CHILDREN

SAMUEL AMBERG

IT has often been stated that enuresis in children yields readily to therapeutic measures of widely different character. But aside from the purely conversational 100 per cent success of certain practitioners, each of these therapeutic measures has to register a considerable number of failures. So it is easily understood that efforts have been made from time to time to classify cases of enuresis in different groups as a basis for treatment. I shall not consider here the incontinence of urine associated with organic lesions of the urinary tract, or nervous system, or the enuresis of the feeble-minded.

The problem of enuresis is really a problem of deranged micturition, even if some of the therapeutic measures are not directly concerned with the restitution of a proper bladder control, but seek to avoid the wetting of clothes and bed by influencing the filling of the reservoir, or by taking up the children during the night to prevent the overflow.

The first difficulty which confronts us in a proper conception of enuresis lies in the fact that the physiology of micturition is not understood. Animal experimentation yielded many very interesting and important results, among which was the discovery by Elliott that the physiologic innervation of the bladder differs in different animals, even as its anatomy differs. Hence, only with great reservations can the experimental results be transferred to man. Further difficulties, particularly for clinical work, arise from the observation that the effect of the stimulation of a nerve depends on the state of the organ which the nerve controls. For instance, it was noticed that the stimulation of the sacral nerve supply produced a relaxation of the bladder when contracted, whereas the same stimulus caused contraction

if the bladder was at rest. Similar differences have been noted in other organs, not only with electric stimulation, but also with regard to the action of drugs. Recent evidence has been advanced to show that the trigonal muscle of man is superimposed on the actual bladder muscles, forming a continuation of the musculature of the ureters, that this trigonal muscle by its contraction opens the orifice of the bladder, and that it possesses a sympathetic nerve supply exclusively. This is of special interest because the opening of the bladder is subject to voluntary control. It is possible to open and close the bladder without calling on the voluntary muscle of the external sphincter. This seems to enter into play only when the desire for urination becomes imperative, although some observations indicate that it may have a greater significance for the maintenance of continence.

The origin of the desire for urination has not been determined further than that it seems to have its source in the muscle wall of the bladder, the mucous membrane having normally no sensation, or very little, and that only in the region of the neck of the bladder. The paths by which the desire for urination is communicated to the brain, and the return paths by which the impulses sent out by the brain travel to the bladder are not known; neither is the mechanism known by which the voluntary opening and closing of the bladder is brought about. Only very recently has it been shown that there is no real anatomic internal sphincter of the bladder in man, but that the surgical or, better, perhaps, functional sphincter is formed by two loops, one of which is derived from the longitudinal, the other from the circular muscle layer of the bladder.

Whether the contraction of the bladder on stimulation of sensory nerves enters into consideration in enuresis is not known. The effect of drugs on this reflex has been studied in animals. It is evident that at the present time our knowledge of the physiology of the bladder is not sufficiently advanced for a proper classification of its disturbances; therefore the division of cases of enuresis into groups must remain more or less haphazard.

Clinically, one of the most striking features of enuresis, as

it is seen under ordinary circumstances, is that in the majority of cases it ceases on the road to, or at about the time of puberty. Relatively rarely does it persist to the end of the period of growth. That certain factors associated with growth may have some connection with enuresis cannot be simply brushed aside. During growth, besides such things as changes in the postion of bladder and spinal cord, many other somatic changes occur, one of the most striking of them being the gradual development of the sexual apparatus. Guyon emphasized the venous engorgement associated with the distention of the bladder, and, dependent on it, the engorgement of the veins of the sexual organs. Furthermore, the vascular and nervous supply of the two systems make the relationship one of more than mere position, and so it would not be strange if the development and function of one exercised some influence on the other.

It has been stated that the cessation of enuresis does not mean that the urinary apparatus is fully restored, because in the history of many later bladder troubles previous enuresis is recorded, and it was thought that the underlying cause of enuresis persisted. This idea has been emphasized particularly in recent years, when the strain and exposure of the war increased the incidence of bladder troubles in adults. Among these patients many had previously suffered from enuresis. Several authors accuse a congenital "Minderwertigkeit" of the urinary apparatus of a rôle in the etiology of enuresis. The familial type of enuresis has found its place here. One of the observations made in soldiers with persistent infantile enuresis, many of whom were intellectually inferior, may be mentioned. In cystoscoping, a diverticulum-like bulging of the fundus of the bladder was often observed. These observations need confirmation, and it would be interesting to know whether a similar condition may occur in children.

The study of enuresis in soldiers has disclosed many interesting facts with regard to changes in bladder pressure, changes in the mechanics of the micturition, and its response to drugs. But how much of this will be of use in our problem remains to be seen. One observation is of great interest, namely, that

colds are capable of eliciting enuresis. While it is known that the majority of patients with enuresis have recovered with the advance of puberty, the time of onset is less certain. Some cases are continued from infancy. In passing, it may be said that the diaper age of most of our children lasts entirely too long. So far as I know, we have no good statistical data showing how often enuresis is transmitted uninterruptedly from infancy; in our experience it has been very difficult to get accurate information from parents on this point. Certain observers believe that in the majority of cases the condition is acquired, that is, the enuresis has a definite onset after the child has had perfect bladder control for some time, about four or five years. Such grouping, for instance with reference to congenital faults, is obviously important, and deserves careful statistical study.

It has been noted repeatedly that enuresis occurs chiefly in children of a neurotic type. While I have had the same impression, a more accurate determination may perhaps cause surprise. In some cases, at least, it may happen that wetting precedes the development of the neurosis, and, indeed, may contribute to its production. That it can contribute to its aggravation directly, or more indirectly, as a result of scolding, and so forth, is fairly certain. The presence and degree of neurosis, naturally, will influence the treatment along the usual lines. A large number of enuretics suffer also from pollakiuria, frequently associated with urgency. This feature of the problem has been particularly emphasized by the school of Guyon, who ascribed most of the cases of enuresis to atony of the sphincter. For this reason he instituted the treatment with the faradic current, applied by means of a special bougie directly to the pars membranacea.

If it had been proved that an anatomic lesion of the spinal cord existed in that group of cases of enuresis which was assigned to myelodysplasia, it would not concern us here. Enuresis is only one of several manifestations of myelodysplasia, such as malformation of toes, disturbance of sensation, and apparently very often, spina bifida occulta. Spina bifida occulta without enuresis is revealed by roentgenograms so often in the Mayo

Clinic that we can hardly attach any significance to it. Indeed, the justification of myelodysplasia as a clinical entity has encountered very serious obstacles.

Many observers regard enuresis as of purely psychic origin, even as a manifestation of hysteria. For instance, according to Janet, all cases not due to epilepsy or atony of the sphincter, that is, in his opinion the great majority of cases, are purely psychic in origin. All of these children have pollakiuria which is transformed, owing to the depth of sleep, into enuresis, which is evoked by dreams of micturition. This dream theory has found favor in many eyes. The depth of sleep does not militate against it, because Janet satisfied himself that dreams do occur in deep sleep. He recalls with approbation the corollary of Henoch concerning pollution which is associated with dreams. The desire for urination impresses itself on the brain, and by its frequency makes the brain more receptive to urinary sensations; hence the dream. But even if it could be proved that enuresis is always associated with dreams, that, by itself, would not prove by any means that these dreams produce micturition. The parallel with pollution seems to be unconvincing, for the erotic dreams associated with this seem to occur only when the activity of the sexual organs calls them forth, and a dream of micturition might just as well be caused by micturition as precede it. The connection of sleep with enuresis has been explained in different ways, including the theory that the depth of sleep interfered with the perception of the bladder sensations, and thereby excluded the control exercised by the central nervous system, or that it was not deep enough, so that the central nervous system acted promptly in response to the urinary sensations, particularly when these were exaggerated. It need hardly be said that in neither case were efforts made to determine the depth of sleep more accurately.

The great variety of treatments which, at times, have been found useful have prompted many to search for a common factor; this was found in the power of suggestion inherent in any therapeusis. Further strength was added to this reasoning by the fact that cases of enuresis yielded to purely suggestive

treatment, such as more or less intensive wake suggestion (Campbell, Pototzky) or hypnosis.

All this greatly strengthened the theory that enuresis is a purely functional disorder of psychogenetic origin. It cannot be denied that many observations point forcibly in this direction. I recall a very striking illustration related to me by Dr. Nassau of the Orphan Asylum in Berlin. A boy wet the bed while sleeping on the ground floor, and ceased to do so on his transfer to an upper floor. On the ground floor were mice, and he was afraid to get up. The upper floor was free from mice, he was not afraid to get up, and it was not necessary for him to do so. It may be that at times psychic elements furnish the preponderant cause of enuresis, at other times they may participate in its production to a lesser extent. It is obviously true, as has been said in criticism of the theory of psychogenetic origin of enuresis, that not every symptom which yields to a psychic influence must be psychogenetic. In this connection I may say that my efforts to treat enuresis in children by hypnosis have not been very successful. Several authors place the age at which hypnotic treatment of children may prove efficacious at different levels. From very limited experience I believe that it may easily prove fruitless during the first decade of life and perhaps the first part of the second. It seems that young children are less amenable to the posthypnotic suggestions, therapeutically so important, but a more extensive observation may show different results.

The danger of overemphasizing the psychic element in cases of enuresis lies in the neglect of other factors, the recognition of which may shed some light on the problem and aid in combating it.

It has been claimed that patients with enuresis do not feel the desire for urination so keenly as normal persons, and that in some cases the faradic irritability of the bladder is diminished. But this phase of the problem was not stressed until Weitz and Götz, testing by means of a manometer the pressure changes in the bladder on introduction of fluid, found that the bladder of patients with enuresis behaved exactly like the bladder of normal

persons in regard to pressure changes, but that there was one very significant difference; the enuretics experienced no desire for urination, or only very little. This desire in the normal person about coincided with the advent of a bladder contraction. This lack of sensation they observed in the majority of enuretics. The results were apparently first obtained from a study of adults, and Weitz continued the study with children. In order to increase the sensitiveness of the bladder, they introduced a certain amount of silver nitrate in strength varying from 1 : 4000 and 1 : 750, keeping it in the bladder for a period of time, and reported excellent results in somewhat more than half of the cases treated. These results were confirmed on the whole for children, but whether by actual experiment or only by treatment is not certain.

Dr. Foucar and I treated some cases of enuresis by this method. At the same time we wished to assure ourselves that it actually led to the establishment of a normal desire for urination. The tests make great demands on one's patience, even with older children, and sometimes it was impossible to carry them out. A few tests were made with the water manometer, but a mercury manometer makes the tracery of curves much simpler. A soft catheter is introduced in the bladder and the urine is allowed to drain. Then a tepid solution of boric acid is run in up to the desired amount, the tube leading to the reservoir is clamped off, and the connection between catheter and manometer is opened after establishing the base line. There is absolutely no danger in this proceeding if carried out properly. Many therapeutic procedures recommended in the treatment of enuresis require the introduction of the catheter, as, for instance, the distention of the bladder. The simple introduction of the catheter has been used with success in the cure of enuresis; this happened in one of our cases in which, on account of the boy's violent objections, we could not pass the catheter as far as the bladder.

In the small number of cases examined thus far we were surprised to find that the lack of sensation described by Weitz and Götz was the exception rather than the rule. The results

of our few cases are very interesting, and invite further investigation.

In Figure 35 (A390449) are shown the results in a boy aged ten years, about 10 per cent underweight, very nervous, easily excited, and not handled properly at home. He suffered from diurnal enuresis, which occurred nearly every day, once or

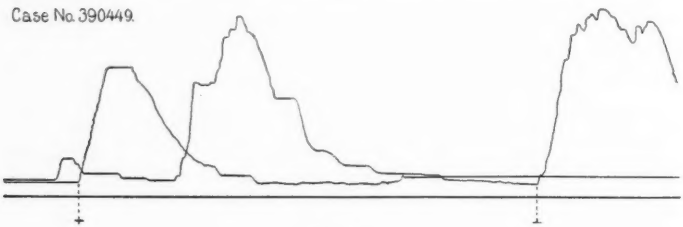

Fig. 35.

several times, particularly when excited or playing. The ailment was supposed to date back to infancy. At the point marked +, the desire for urination was signified, and, as it is seen, coincident with it a very marked contraction, and it may be noted that this happened each time the contraction occurred. The curve corresponds to the description of the norm given by

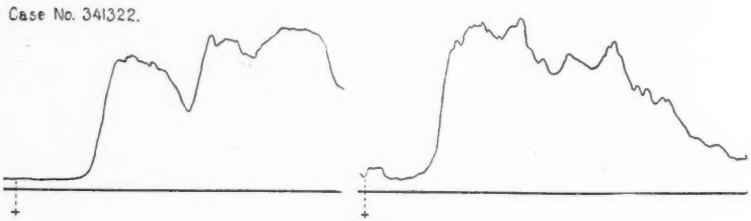

Fig. 36.

Weitz and Götz. A little fluid escaped by the side of the catheter, and one must be careful that such happenings are not translated by the child into a desire of urination. (The illustrations show two sets of curves because the drum was allowed to revolve twice.)

In Figure 36 (A341322) are shown the results in a boy aged eight years, who wet himself at night if not taken up. He once

went for a period without wetting, and once wet himself in the daytime. He is hard to waken. Again each contraction was

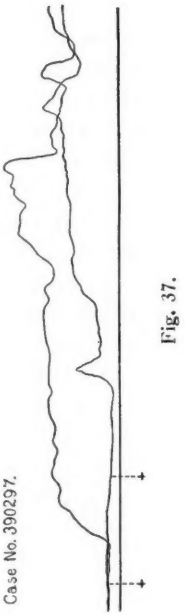

Fig. 37.

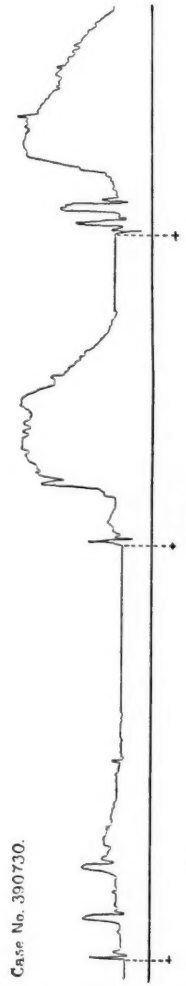

Fig. 38.

preceded by the desire of urination, but there was a latent period.

Figure 37 (A390297) gives the results in a girl, aged nine years, in whom enuresis, chiefly diurnal, started at the age of five. Once or twice a week she wet the bed. After a severe cold three months before she had wet the bed almost every night, and during the day she had urgency, and wet occasionally. Desire preceded every contraction, but there was a long latent period, and much fluid escaped beside the catheter.

Figure 38 (A390730) represents a case of special interest. A girl, aged six years, nervous and excitable, wets if not taken up about three times in the night. During the day she has urgency. Much fluid escaped by the side of the catheter. With each contraction desire is pronounced; but in one instance in the illustration, and at other times, with the desire, there came a down stroke on the curve. The same phenomenon, fall in pressure, was seen in another case of enuresis in a little boy five years old, who also had good sensation. In the case of the little girl the desire for urination was practically coincident with some oscillations of pressure before the real contraction set in, and in one instance, as seen in the curve, there were only these oscillations.

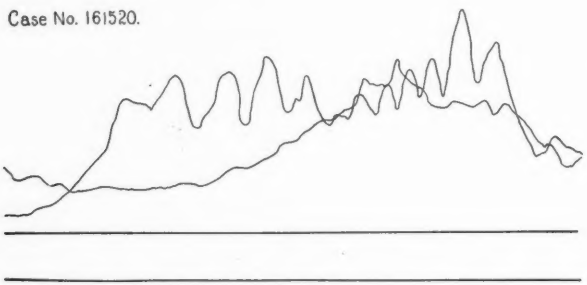

Fig. 39.

Figure 39 (A161520) was obtained from a boy aged six years, who, since infancy, had wet the bed nearly every night, one or more times. In this case absolutely no desire to urinate existed. A similar lack of desire was found in another boy eight years of age, a nervous lad about 15 per cent under weight, with

diurnal and noctural enuresis, occurring almost daily. Here there was no sensation whatever, even with excessive filling of the bladder. The contractions were less pronounced than in the other cases.

Unfortunately, we had no opportunity to take tracings from normal children at various ages, and cannot say whether the latent period intervening between the desire for urination and the contraction of the bladder is peculiar to enuresis. At any rate it is evident that the desire for urination can precede the contraction of the bladder, and therefore is not dependent upon it, as has been claimed. The drop of pressure in the bladder with the desire for urination is difficult to explain. It can hardly be a coincidence.

Even if the number of enuretics with absence of sensation is not as great as believed by Weitz and Götz, it seems to be a very tangible group, demonstrating a definite fault in the mechanism of micturition.

It may be mentioned that none of these patients had spina bifida occulta, and that none of them yielded either to distention of the bladder or to the silver nitrate treatment. Neither was the psychic influence of the treatment sufficient to effect a cure.

In one case the enuresis could be controlled by rest in bed. We were unable to get urine collections, so cannot say whether this case belongs to the interesting group described by Bossert-Rollett. In some cases of enuresis she found that more urine was excreted at night than during the day, and in some of these cases rest in bed changed this condition to the norm, so that less urine was excreted during the night and the enuresis ceased. In these cases a certain weakness of the circulation was assumed from a weakness of the first heart sound. This was not observed in our case.

Another effort at grouping cases of enuresis was made by Lippmann, who gave his patients a given amount of fluid to drink, and determined the amount voided, one day after they had stood upright for three-quarters of an hour, and in another day after they had been lying on their backs in the most comfortable position, the legs drawn up and the upper part of the

body elevated so that a marked kyphosis resulted. This is the position most favorable for diuresis. In some cases the difference in the urine secretion was more than 200 c.c. on an intake of 300 c.c. In these cases in which the children wet the bed shortly after falling asleep, it has proved sufficient to let them lie in bed in the position indicated for about an hour, and empty the bladder before going to sleep.

The groupings of Bossert-Rollett and of Lippmann also await confirmation on a larger scale. These efforts at differentiation are certainly very helpful, even if they do not strike so much at the root of the evil, but rather are directed toward avoiding the filling of the reservoir to the point where it demands relief. This may be accomplished in various ways by the dry diet of Nobel, or by a diet indicated by the result of Rietschel, who was able to delay the excretion of urine very considerably by a diet rich in carbohydrates and salt.

SUMMARY

A better conception of the physiology of micturition is absolutely essential for a better understanding of enuresis in children. Experiments show that certain differences in bladder sensation and contraction can be demonstrated.

CERTAIN UNUSUAL FEATURES NOTED IN A CASE OF INOPERABLE CANCER OF THE BREAST TREATED BY ROENTGEN RAYS

ARTHUR U. DESJARDINS

ROENTGEN-RAY treatment of cancer of the breast, in conjunction with surgery in operable cases, and independently, when the cancer is too extensive to permit complete surgical amputation, is being used extensively with more or less benefit to many patients. In certain cases large primary tumors with extensive involvement of the tributary lymphatics disappear completely under this treatment; in others the process may be checked for varying periods, surface ulceration prevented, and the subsequent evolution of the lesions more or less delayed until death occurs from metastatic invasion of vital organs.

The effect of radiation on cancer cells seems to vary according to many factors, such as the predominating type of cell, the rate of growth based on mitotic activity, the determining cause of which is unknown, the efforts at resistance by the tissue in which the new growth is developing, the degree of differentiation of the malignant cells, and so forth.

When a malignant tumor is examined histologically some time after thorough treatment by radiation it is customary to find marked and sometimes complete destruction of the cells; often, however, while cellular destruction may be very great, certain cells or small groups of cells, either because they are better able than others to withstand the effect of the rays, or because they receive a smaller dose, retain their viability amid an increasing mass of connective tissue, newly formed to replace the degenerated cells. Gradually these cells, whose power of proliferation has been more or less diminished, recover some of this power and resume their destructive activities. This is particularly true in tumors of considerable size. In many

early tumors the growth momentum of whose cells has not had time to reach its maximum, thorough radiation is less likely to be followed by recurrence, because at this stage the malignant cells are more vulnerable. However, it is during this early stage of cancer that surgery has its only opportunity of curing the patient, and since complete and wide surgical ablation, when possible, offers a good chance of cure, it is and will remain for some time the treatment of choice. Unfortunately, a large percentage of persons with cancer of the breast, presenting themselves for examination, have fairly extensive lesions with involvement of axillary, infraclavicular and, too often, of supraclavicular glands. In the presence of such extensive neoplastic dissemination it is impossible for the surgeon to accomplish the wide excision required if the patient is to have reasonable hope of remaining free from recurrence.

The radiologist, when called on to treat a neoplasm that has previously been subjected to incomplete operation, knows from experience that such a tumor often behaves as if it had been stimulated to increased activity, and that it will not yield to radiation with the same readiness as a tumor not so stimulated. In view of the commonly pernicious effect of incomplete operation, and of the not infrequent striking improvement following roentgen-ray treatment in frankly inoperable cases, it would seem wise to withhold operation whenever clinical examination reveals a degree of involvement in which wide excision is impossible. In this connection the case I shall present is interesting, not only because it shows the striking effect of radiation on cancer, but because it serves to demonstrate another phase of the application of roentgen rays to the treatment of cancer of the breast.

Case A403891, Miss C. M., aged forty-four years, came to the Clinic September 5, 1922, seeking relief from a large mass in the left breast. Six months before she had first noticed in this breast a lump, which had grown steadily. She did not consult a physician until three weeks before coming to the Clinic, when she was told that the condition was malignant, and that the axillary glands were enlarged. The left nipple had never been as prominent as the right, but the patient thought it was more retracted than formerly.

On examination, the left breast was found to be a solid mass with moder-

ate retraction of the nipple and a glazed appearance of the skin (Fig. 40). The portion beneath the upper, outer quadrant was particularly hard. In the left axilla there were three glands, the largest one measuring 4 by 2 cm., and the smallest being 1 cm. in diameter. In the left infraclavicular region another gland, 2 by 1 cm., could be palpated, and above the left clavicle two other glands, 1.5 and 1 cm. in diameter, respectively. The condition was considered inoperable and the patient was referred for radiation treatment. The patient weighed only 86 pounds (her normal weight) and the thoracic wall was rather thin; it is of importance to bear this in mind in connection with some of the subsequent features of the case.

Fig. 40 (A403891).—Massive left breast with retracted nipple before treatment. Axillary and supraclavicular adenopathy not very evident except on palpation.

Between September 11th and 18th an extensive course of roentgen-ray treatment was given, the distribution and plan of which are shown in Figure 41. The dose was:

Voltage	135 kilovolts (peak) measured by the sphere-gap method
Focal skin distance	40.5 cm.
Filtration	0.05 mm. copper and 0.1 mm. aluminum
Milliamperes	5
Time	1 hour and 30 minutes

This dose was administered to each field, the beams directed to the left breast being focused as shown in the diagram. The skin toleration to this dose was very good, and it was repeated between October 16th and 25th.

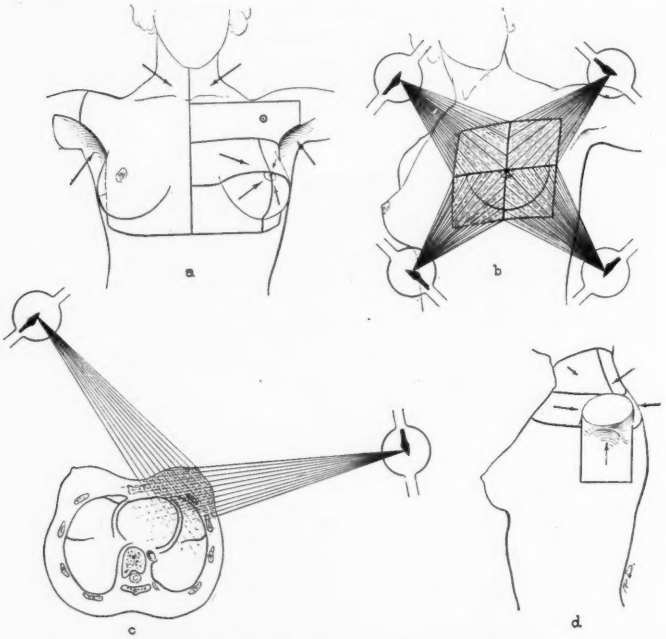

Fig. 41.—Showing plan of treatment: *a*, Distribution of the fields through which the treatment was given. The arrows indicate the direction in which the beams of *x*-rays were focused in each case. It will be seen that the involved left breast had four beams concentrated on it, each beam being focused at an angle of approximately 45 degrees. Three beams were focused to the axillary and infraclavicular regions, one from the front, one from the axillary aspect, and one from the back (see *b* and *d*). Two beams were focused to the supraclavicular region, one downward, inward, and backward from the front, and the other downward, inward, and forward from the back; *c* shows the crossing of the beams through the breast and also shows that the point of crossing of the four beams directed to the left breast must have delivered a considerable dose to the underlying pleura and lung surface.

November 17th, the condition of the breast was very much improved; its substance was much softer; the left supraclavicular and infraclavicular glands were no longer palpable, and the left axillary glands had diminished in size

Fig. 42 (A403891).—Cluster of malignant skin nodules on left side

Fig. 43 (A403891).—Patient immediately after treatment. Note comparative appearance of breasts and nipples.

40 to 50 per cent. In the left posterior axillary line was a cluster of cutaneous and subcutaneous metastatic nodules (Fig. 42).

Between November 21st and 23d, a third course of roentgenization was given, but this was limited to the left half of the thorax and the dose was changed so as to have greater effect superficially, and less on the deeper structures. The treatment factors were:

Voltage	135 kilovolts (peak)
Focal skin distance	40.5 cm.
Filtration	0.6 mm. aluminum
Milliamperes	5
Time	40 minutes

December 23d another and still more superficial dose was delivered to the area corresponding to the cluster of skin nodules mentioned. Between January 23d and 27th, a course of treatment with full dosage was given, and by March 6th the condition, so far as the breast and metastatic glandular involvement was concerned, as well as the area of skin nodules, was entirely satisfactory. The axillary, infraclavicular, and supraclavicular glands, and the skin nodules had entirely disappeared (Fig. 43).

DISCUSSION

This case demonstrates that roentgen rays can exert a pronounced influence on cancer. I am not attempting to convey the impression that the patient in this case is cured, but she has been tremendously benefited. There is another extremely interesting phase of this condition. It has been known for some time that, in a small number of patients with cancer of the breast, treated by intensive roentgenization, a varying degree of pleural reaction is produced in the zone beneath the treated area. Considering the total number of cases treated, this occurs but rarely. I have seen it in four cases, and in each instance, the patient was small, with thin thoracic walls. In the case reported here, following the course of treatment in January, the patient developed noticeable pulmonary symptoms. She had had a cold with cough for some time, and suddenly developed a fairly sharp rise in temperature; the cough increased, and she began to expectorate blood-streaked mucus. For a few days this seemed rather serious, but gradually the symptoms subsided. The physical signs in the left lung were not those of pulmonary abscess and the clinical features did not resemble those of abscess of the lung. January 25th a roentgenologic

examination of the thorax brought the report "thickened pleura, left base; very extensive infiltration, lower left lobe; possible abscess" (Fig. 44). However, the patient's condition steadily improved, and February 26th another roentgenologic examination of the thorax revealed a quite different picture. There was still

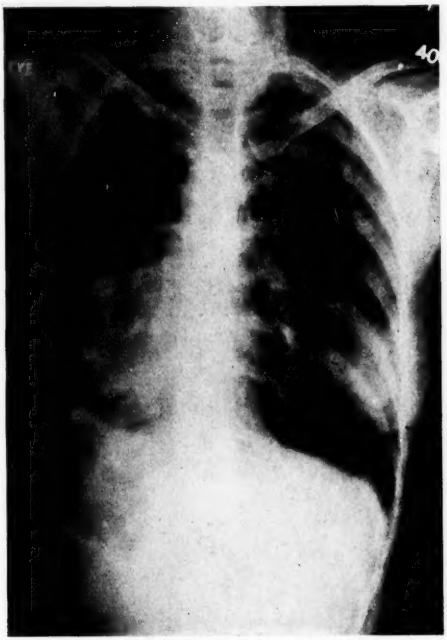

Fig. 44.—Roentgenogram of the thorax January 25, 1923. Area of infiltration with central clear space, suggesting abscess. Possibility of metastatic process considered.

pleural thickening around the left base, but it was limited to the periphery, and the infiltration previously mentioned had disappeared. The heart was drawn somewhat to the left; the condition was clearly a chronic fibrous process in the pleura (Fig. 45). In view of the four beams of roentgen-rays focused so as to cross-fire the left breast, on three different occasions,

and in view of the thinness of the thoracic wall in this patient, the subsequent events are entirely accounted for, but during the height of the reaction the symptoms and physical findings, and the first roentgenogram, were not easy to interpret. It was necessary to consider the association of metastasis and acute

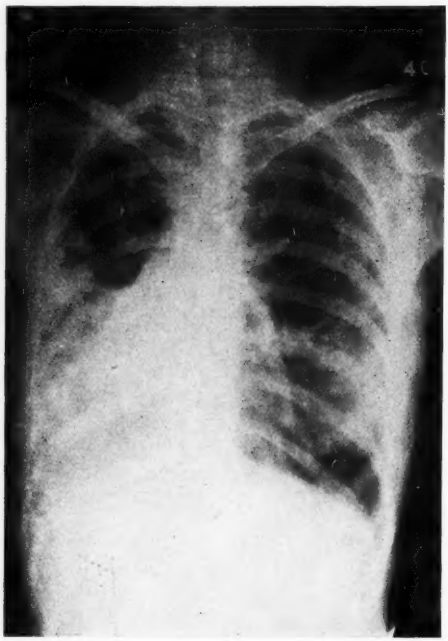

Fig. 45.—Roentgenogram of the thorax February 26, 1923. Dense fibrosis of the pleura.

pulmonary disease, and it was only later that a correct estimate of the situation could be made.

So far as the effect of radiation on this group of tumors is concerned, this case is not at all exceptional; many others have been treated with more or less similar results depending on the nature and extent of the primary lesions. If roentgen rays can exert such astonishing action on inoperable neoplasms there

seems to be no reason why like effects cannot be obtained in the operable group.

It is still too early to form an accurate estimate of the exact effect radiation treatment may finally prove to have on the statistics of cancer of the breast. Intelligently applied, it may prove of even greater service in operable cases than it is now in the inoperable.

REPORT OF THREE CASES: ADENOCARCINOMA OF THE OVARY AND TUBE WITH TUBERCULOSIS, FIBROMYOMA IN HERNIAL SAC, AND SOLID CARCINOMA OF THE LEFT OVARY

LEDA J. STACY
AND
OLIVER C. MELSON

Case 1 (A412804), Mrs. J. H., aged thirty-nine years, came to the Mayo Clinic December 13, 1922, complaining of a profuse, gradually increasing, watery vaginal discharge of eighteen months' duration. She described the discharge as having the appearance of urine, and at times a uriniferous odor. In fact, vesicovaginal fistula had been suspected but not demonstrated. At times the discharge was so profuse that the patient thought something inside had burst. There was never any blood in this discharge, and since its onset the menstrual periods had decreased in duration and amount. The patient had been married fourteen years without a pregnancy. The menstrual periods were established at fourteen and were profuse. In 1920 appendectomy was performed (elsewhere) after a clinical diagnosis had been made of right ovarian tumor. Her previous history was in other respects inconsequential.

Examination revealed a profuse, watery, colorless discharge from a rather soft cervix. The fundus of the uterus was small and freely movable. In the left pelvis was a cystic mass about 5 cm. in diameter, which was movable to a limited degree and moderately sensitive. A cystoscopic examination was made which proved negative. The absence of creatinin, and only a faint trace of uric acid proved conclusively that the fluid was not urine. A clinical diagnosis of left cystic ovary and hydrosalpinx was made, and exploration of the pelvis was advised.

December 23, 1922, separation of extensive adhesions of the omentum in the pelvis revealed the left tube to be 7.5 cm. in diameter, and adherent to the ovary, which was cystic. The right tube was smaller, and the right ovary apparently normal. The uterus, both tubes, and the left ovary were removed. On pathologic examination it was found that both tubes were involved by a chronic tuberculous process; the left was closely adherent to the ovary, and, besides containing a papillary carcinoma, was tuberculous. Examination of the uterus revealed a polypoid endometrium, multiple myomas, and marked sclerosis of the vessels.

The patient recovered uneventfully, and was dismissed from the hospital on the twenty-fifth day. Radium and roentgen-ray treatment was recommended as a postoperative procedure, and before the patient was dismissed from observation 1400 milligram hours of radium and six roentgen-ray treatments were administered. In March, 1923, there was no evidence of recurrence of the pelvic tumor.

Comment.—Prior to operation we were of the opinion that this condition might be a hydrosalpinx discharging, from time to time, a portion of its contents. From the findings at the operation it might be considered an example of the uncommon condition, primary carcinoma of the fallopian tube. The history is quite typical of this, but because of the close association of the tube and ovary and because both were found to be malignant, it is difficult to determine which is the primary growth. Another interesting feature of this case is the association of tuberculosis with malignancy. Both tubes contained tubercles which, however, were apparently quiescent.

Case 2 (A421671), Mrs. J. T., aged forty-seven years, came to the Clinic April 2, 1923, complaining of a large hernia in the right inguinal region. The hernia had appeared six years before, after a fall from a ladder. For a time it was easily reducible, but for the last two years it had not been possible to get all of the tumor inside the abdomen. The patient thought the hernia had been growing rapidly during the past winter, and it was giving her great inconvenience in walking. She had had some difficulty in urinating recently.

The general examination revealed a large inguinolabial hernia on the right side, 22 x 13 x 13 cm. The pelvic examination was practically negative. A clinical diagnosis of right inguinolabial hernia was made.

At operation a degenerating fibromyoma of the round ligament, weighing 1370 gm., was removed from the hernial sac. The wound was closed by bringing the internal oblique and external oblique muscles to Poupart's ligament, and imbricating the lower layer of the external oblique on top of the upper. The pathologic report revealed this to be a single, degenerating, myxomatous fibromyoma (extraperitoneal—Fig. 46).

Case 3 (A424715), a girl, aged fifteen years, came to the Clinic for examination May 4, 1923, because of a growth in the abdomen, first noticed in August, 1922. Menstruation had been established at the age of thirteen, and had been irregular until six months before examination. The flow was not excessive, lasted about a week, and there was always dysmenorrhea, although it had become less recently. From the onset of menstruation, the patient had had fainting attacks, felt weak, suffered with constipation, and had difficulty in urinating during her periods. In August, 1922, she noted a small movable tumor in the lower abdomen, which grew noticeably. For four months she

had had no difficulty in urinating, and no fainting spells. Constipation had increased recently, and there was a dull aching in the region of the tumor. She had lost some weight and strength, and had been coughing for a week or two.

Examination revealed a large, hard, rather fixed, nodular pelvic tumor extending well above the pubis. The cervix was high against the pubic bone. A clinical diagnosis was made of uterine tumor, probably sarcoma, and exploration was advised.

At operation was found a tumor of the left ovary, as large as an eight months' pregnancy, densely adherent and impacted behind the uterus. Grossly, it was malignant, and therefore, a total hysterectomy with bilateral

Fig. 46.—Fibromyoma in hernial sac.

salpingo-oöphorectomy was performed. No metastasis to the liver or glands was noted. The pathologist reported solid carcinoma (18 by 13 cm.) of the left ovary, involving the uterus and left tube. The patient was in fair condition immediately after the operation, but by midnight she was delirious, the pulse was rapid, and death occurred at 5:15 a.m. Necropsy revealed metastasis to the aortic lymph-nodes.

Comment.—The youth of this patient is especially noteworthy. Hoon has reported solid carcinoma of the ovary in one patient, aged eight years, and another sixteen. It is also of interest that the postmortem examination revealed involvement

of the aortic lymph glands, although a careful search at the time of operation disclosed none. One point in the clinical history might be suggestive in considering the cause of this tumor. The patient had fallen at the age of ten, striking on the abdomen, and was unconscious for a short time, but recovered from this without any apparent sequelæ.

THE TREATMENT OF THREE CASES OF CHRONIC ADDISON'S DISEASE

LEONARD G. ROWNTREE

IN the spring of 1920 Doctor A. L. Muirhead, Professor of Pharmacology, Creighten Medical School, Omaha, appealed to me by letter for advice relative to the treatment of Addison's disease, of which he claimed to be a victim. After duly considering his letter and his previous clinical record (for he had formerly been a patient at the Mayo Clinic), I advised him to come to Rochester for observation and study. On arrival, careful consideration was directed to the existing conditions, and to the treatment to which he had already been subjected. In conference it was decided to adopt a régime involving the use to the pointof tolerance of epinephrin hypodermically and by rectum, and of desiccated suprarenal extract by mouth. It was further agreed that the doctor himself was to keep detailed records of the results of the treatment, and he was furnished with an apparatus for the study of his blood-pressure. Most gratifying temporary improvement resulted, so gratifying, indeed, that he described his experiences in the Journal of the American Medical Association under date of March 5, 1921, under the title of "An Autograph History of a Case of Addision's Disease." Unfortunately, the improvement lasted but a few months. The subsequent course of the events leading up to the patient's death were outlined by me in the Journal of the American Medical Association.[4] Since Dr. Muirhead's visit we have had the opportunity of applying this régime, to which we now refer as "The Muirhead treatment," to several other patients suffering from acute and chronic types of Addison's disease.

One of the striking results of the treatment of Dr. Muirhead was the clearing up of the pigmentation which was, on admission, quite marked. In the study of his case we experienced considerable difficulty in determining from day to day the degree of pigmentation, the doctor constantly insisting that his skin was becoming lighter in color. It seemed highly desirable, therefore, to secure some one method of determining and permanently registering the degree of pigmentation. Consequently, I undertook to develop a clinical tintometer for the study of pigmentation in this disease and, later, in certain other diseases.

Here we are dealing with a clinical study of three cases of Addison's disease subjected to the Muirhead régime. A certain degree of success has been obtained in all of them, sufficient, I believe, to justify the presentation of our results. In discussing the treatment of this disease, in which the outcome is almost invariably fatal, it behooves us to keep in mind (1) that in the natural course of the disease remissions, spontaneous in character, occur at times; (2) that excellent temporary results have been obtained by others from organotherapy in isolated cases of this affection; and (3) that we should approach the subject in something of the same spirit of humility and restraint which characterized Addison in his classic description of this disease. Because of the striking contrast of his attitude to that of most publications in the field of endocrinology, I am taking the liberty of quoting rather freely from his original article.

"It will hardly be disputed," he says, "that at the present moment the functions of the suprarenal capsules, and the influence they exercise in the general economy are almost or altogether unknown. The large supply of blood which they receive from three separate sources; their numerous nerves derived immediately from the semilunar ganglia and solar plexus; their early development in the fetus; their unimpaired integrity to the latest periods of life; and their peculiar gland-like structure, all point to the performance of some important office; nevertheless, beyond an ill-defined impression, founded on a consideration of their ultimate organization, that, in common with the spleen, thymus, and thyroid body, they in some way or other minister

to the elaboration of the blood, I am not aware that any modern authority has ventured to assign to them any special function or influence whatever.

"To the physiologist and to the scientific anatomist, therefore, they continue to be objects of deep interest; and doubtless both the physiologist and the anatomist will be inclined to welcome and regard with indulgence the smallest contributions calculated to open out any new source of inquiry respecting them. But if the obscurity which at present so entirely conceals from us the uses of these organs justifies the feeblest attempt to add to our scanty stock of knowledge, it is not less true, on the other hand, that any one presuming to make such an attempt ought to take care that he do not, by hasty pretensions, or by partial and prejudiced observation, or by an overstatement of facts, incur the just rebuke of those possessing a sounder and more dispassionate judgment than himself.

"Under the influence of these considerations, I have for a considerable period withheld, and now venture to publish, the few facts bearing upon the subject that have fallen within my own knowledge, believing as I now do, that these concurring facts, in relation to each other, are not merely casual coincidences, but are such as admit of a fair and logical inference, an inference that, where these concurring facts are observed, we may pronounce with considerable confidence the existence of diseased suprarenal capsules.

"It was while seeking in vain to throw some additional light upon this form of anemia (idiopathic or pernicious) that I stumbled upon the curious facts which it is my immediate object to make known to the profession; and however unimportant or unsatisfactory they may at first sight appear, I cannot but indulge the hope that, by attracting the attention and enlisting the coöperation of the profession at large, they may lead to the subject being properly examined and sifted, and the inquiry so extended as to suggest, at least, some interesting physiologic speculation, if not still more important practical indications.

"The leading and characteristic features of the morbid state to which I would direct attention are: anemia, general languor

and debility, remarkable feebleness of the heart's action, irritability of the stomach, and a peculiar change of color in the skin, occurring in connection with a diseased condition of the 'suprarenal capsules.'"

In September, 1922, at a meeting of the staff of the Mayo Clinic, I had the unusual opportunity of presenting three patients whom we believed to be victims of Addison's disease, two of whom had been under study in the hospital for a period of weeks, while the third was undergoing his initial examination in the Clinic. In all three cases the pigmentation was striking, being definitely marked in the naturally pigmented areas, the face, neck, nipples, axillæ, and genitalia, and over the areas subjected to pressure and friction, namely, the buttocks, knees, elbows, spinal column, and so forth. In one case the pigmentation was amber rather than brown; in another the color resembled that of a mulatto; while in the third, the color in many parts was that of the negro. The pigmentation in two of the three cases will be discussed in more detail later.

In all three cases the other cardinal features of Addison's disease, asthenia, gastro-intestinal crises, and unusually low blood-pressure, were present. In all of them the diagnosis clinically was unquestionable. In one case we have an instance of Addison's disease, secondary to syphilis, an unusual case presenting peculiar exacerbations following arsphenamin injections.

REPORT OF CASES

Case 1 (A401101). J. B. L., a man aged twenty-six years, of excellent habits, presented himself at the Mayo Clinic August 10, 1922, complaining chiefly of pigmented skin and weakness. His family history was negative. His past history included measles, mumps, whooping cough during childhood; pleurisy and emphysema with rib resection in 1900; pneumonia again in 1906; malaria (questionable) in 1921. In 1921 the patient had developed a peptic ulcer, the onset being sudden and associated with severe pain in the abdomen, followed by hemorrhage and melena. He was kept in bed on an ulcer régime for a period of eight weeks. In February, 1922 he first noticed pigmentation, the face and neck gradually becoming darker, and always appearing dirty. His illness has been continuous since, with weakness and occasional spells of mild dizziness, particularly on straightening up suddenly. He weighed 129 pounds, having lost 36 pounds during the course of nine months.

At examination, systolic blood-pressure was 105, and diastolic 75. The

pigmentation ranged from brown on the arms to black on the genitalia. There was a small area of pigmentation on the lower gum. The face and the margins of the lip showed small black areas. Over the back was a scar in the region of the ninth rib in the left axilla. The laboratory findings revealed the hemoglobin to be 80 per cent (Dare), the erythrocytes, 4700; the leukocytes, 4300; lymphocytes, 41; large mononuclears, 2; transitionals, 5.5; neutrophils, 48; eosinophils, 3, and basophils, 0.5. One hour after a fractional test meal, 190 c.c. of gastric contents were withdrawn; a total acidity of 34, and free hydrochloric acid of 18 were noted. The basal metabolic rate was −10. Roentgenograms of the chest and of the stomach were negative. The patient was seen in consultation in the dermatologic section where the pigmentation was diagnosed "Addisonian" in character. He was sent to the hospital where he was placed on glandular treatment consisting of from 2 to 15 min. epinephrin 1 : 1000 hypodermically, once or twice a day, 1 c.c. in salt solution twice a day by rectum, and 5 gr. dried desiccated whole gland, by mouth, three times a day. During the first few weeks the blood-pressure ranged from 90 to 125 systolic and from 50 to 80 diastolic, being 130 systolic and 80 diastolic on dismissal. Epinephrin was given hypodermically and by rectum to the point of tolerance. The patient improved steadily, having gained 20 pounds in weight. His color is somewhat better, and he has had little trouble with his stomach.

A letter received April 12, 1923 says, "It seems to me that I am improving all the time and am much lighter in color than I have been for from two to three years. My wind is not what it should be, but I can see a great change for the better. I am taking the same amount of medicine prescribed by you last summer. I am quite active, sleep well eight to nine hours; I am still under the care of a physician." His physician reports the case as follows: weight 145 pounds, strength not entirely returned to normal, indigestion occasionally, systolic blood-pressure 106 to 108, and disatolic 62, pigmentation decreased, but still marked, appetite good, some shortness of breath.

Case 2 (A403755). W. W., a locomotive engineer, aged fifty-three years, came to the Clinic September 4, 1922 because of the dark discoloration of the skin, and of attacks of generalized weakness. His family history was negative. He had had diphtheria at the age of six, pneumonia at twelve and thrteen, gonococcal infection at eighteen, and ten years prior to his visit to the Clinic an accident in which he jumped from his engine while traveling at the rate of twenty-five miles an hour. Although no fractures were incurred, the patient was laid up for thirty-two days thereafter. In November, 1920 a polyp was removed from the rectum. Since childhood he has suffered intermittently from bilateral frontal headaches. The present illness began in November, 1920, with spells of weakness, centering chiefly in the abdomen. Somewhat later generalized "yellow jaundice," including the conjunctiva, was noted. After this cleared up a dark pigmentation appeared. May 19, 1921 the patient became ill and so weak that he was forced to discontinue work; he gave up "firing" for four months. Subsequently he "fired" for only eight to ten days a month. For the six weeks prior to his visit he had not worked. At first his appetite was very poor, and vomiting

marked, but he craved sour foods. At the time of examination he said that his appetite was fair. Constipation had been present since the onset of pigmentation. Before the onset of the trouble his weight was 160; his present weight was 125. The patient described his distress as akin to a feeling of weakness and hunger. Dyspnea was apparent on exertion, but there was no palpitation or edema. The patient slept only fairly well; nocturia occurred once or twice.

Physical examination revealed marked pigmentation generalized over the entire body; in fact, the skin was as dark as that of a negro, but the discoloration was most marked over the genitalia and about the buttocks; it was slight over the hard palate, and was quite marked in the buccal mucous membranes. The systolic blood-pressure was 80, and the diastolic 58; the pulse was 72, and the temperature 98.6. Urinalysis revealed nothing abnormal. The hemoglobin was 70 per cent (Dare), the erythrocytes numbered 4,600,000, and the leukocytes 6000. The Wassermann reaction was negative. Roentgenograms of the chest disclosed old tuberculosis in the right upper lobe, and marked hypertrophic arthritis in the lower lumbar spine. The basal metabolic rate was −4. The head of the section to which he was admitted made the following notation on the history, "Unless the Wassermann reaction is positive, ought not to be held here, as condition is in advanced stage."

The patient was under observation from September 4 to 18, 1922. He was hospitalized and placed on a treatment consisting of whole gland by mouth, 10 gr. three times daily, epinephrin 1 : 1000 1 c.c. in normal salt solution by rectum three times daily, and 5 min. in 1 : 1000 hypodermically, once or twice daily. At the end of one week he said that he felt 30 per cent better, that he was hungry on a caloric intake of 3500, and that talking and walking no longer tired him as formerly. He has continued his treatments at home to the best of his ability, although he has considerable gastric upset which he ascribes chiefly to the desiccated gland. Almost monthly letters have been received, and these indicate rather definite improvement. In November he wrote that he was working three days a week; in February that he was working part of the time and had gained up to 129 pounds; in March that he had an attack of the "flu" which upset him considerably; in April that he was feeling better, although his weight had dropped to 120 pounds. We have written to his doctor, asking him to put the patient through another course of intensive treatment.

Case 3 (A387986). P. A. Y., a salesman, aged thirty years, was admitted to the Clinic April 3, 1922. His family history was negative. His past history included appendectomy ten years before for acute appendicitis, and a severe attack of influenza in 1918, at which time he was in bed for fifteen days. At this time, dilatation of the right pupil was noted which has since persisted. His recovery was rapid and complete. He had had his tonsils and two infected teeth removed. His present illness began a year and a half before examination, after an influenzal infection, when he began to lose weight gradually and progressively, and to lose strength. He had suffered from obstinate constipation, with frequent bloating of the stomach during the last few months. His appetite had failed, and he had had some quantitative

food distress. His color had become sallow, and his tongue sore, with slight pigmentation of the mucous membrane. He had worried considerably about himself. He weighed 150 pounds; formerly he had weighed 201. On physical examination the knee-jerks were rather inactive, but could be obtained. A few acne spots were scattered over the back, and the mobility of the lumbar spine was somewhat restricted. On first examination the systolic blood-pressure was 100, and the diastolic 70; the pulse and temperature were normal. A slight trace of albumin and a few hyaline casts were found in the urine. Examination of the blood revealed a hemoglobin of 75 per cent (Dare), erythrocytes, 5,070,000; leukocytes, 13,500; lymphocytes, 40.5; mononuclears, 2.5; transitionals, 3.5; neutrophils, 47.5; eosinophils, 4.5; and basophils, 1.5. Three weeks earlier the leukocytes were said to have numbered 17,000. The Wassermann blood and spinal fluid reactions were strongly positive. Roentgenograms of the colon, chest, lumbar spine and sacro-iliac regions, and of the stomach were negative. The color was sallow rather than brown. When I first saw the patient he did not impress me as being a victim of Addison's disease, although we gave the question serious consideration. No explanation was found for the leukocytosis or lymphocytosis.

The patient was placed on treatment for syphilis and carefully watched by the syphilologists. His hypotension was extreme at times, systolic 78, and diastolic 40. This low pressure, together with loss of weight and strength and an increased pigmentation, inclined the physicians to a diagnosis of Addison's disease, and caused them to proceed with the treatment for syphilis cautiously. During the next two months the patient continued to lose weight, which decreased to 130 pounds. He came under my observation July 14, 1922, and was admitted to the hospital July 19th, at which time he was placed on the Muirhead régime for the treatment of Addison's disease. Almost immediate improvement was noted; he had a better appetite and felt brighter and stronger. There were no cramps or diarrhea. He said that he had gone through previous periods of great weakness and spontaneously became stronger at times. August 26th the systolic blood-pressure was 122, and the diastolic 82, but it fluctuated from day to day, being as low as 94 systolic, and 54 diastolic. The basal metabolic rate varied from -4 to $+3$, but under the administration of epinephrin it increased within half an hour to $+35$. The ill effects of the arsphenamin were overcome almost completely by the subcutaneous injection of 0.5 c.c. of 1 : 1000 epinephrin solution before, or at the time of the injection of arsphenamin.

In November, 1922 the patient returned home and continued to improve. He gained from 8 to 9 pounds in weight, his color became much better, and he worked half-days, although he tired easily. He said that he was continuing the administration of 0.5 c.c. 1 : 1000 solution of epinephrin by rectum, and 5 gr. desiccated suprarenal extract three times daily by mouth. His appetite had improved and he had gained in strength. The pigmentation of the tongue was much less than formerly. The systolic blood-pressure at the end of November was 120, the diastolic 80. No digestive upsets had occurred.

In February, 1923 the patient revisited the Clinic. At this time his weight was 135.5 pounds; the systolic blood-pressure was 98, and the dias-

tolic 64. His condition was remarkably improved, and his color was almost normal. He was again subjected to treatment for syphilis, but without any protection by epinephrin, and marked digestive disturbances with excessive vomiting and great weakness followed. His extreme prostration compelled him to stay in bed. These symptoms cleared up in the course of a week under the administration of the Muirhead régime, and subsequently he has continued arsphenamin treatments without mishap, taking min. viij epinephrin by hypodermic daily, 1 c.c. by rectum twice daily, and 5 gr. of the whole gland by mouth three times daily.

DISCUSSION

Unpleasant symptoms, the so-called nitritoid crises, following the administration of salvarsan, and consisting of headaches, flushing, dyspnea, vomiting, precordial pain, backache and diarrhea, and occasionally of apoplexy, have been described. Such crises have been attributed to marked vascular dilatation, and in such conditions the administration of epinephrin has been advocated either at the time of the injection or preceding it by about ten minutes. Exanthems following neosalvarsan can be prevented in the same manner, according to Naegeli.

Professor Hata, who saw this patient with me during the recent visit to the Clinic of the Japanese Commission, regards the nitritoid reaction as probably anaphylactoid in type. In explanation of it he said that a salvarsan injection into the bloodstream of rabbits causes a decrease of adrenalin-like substances in the blood. Repeated injections result in a higher content of adrenalin in the suprarenal glands, but a lower content in the blood; that is, adrenalin is held in the gland itself, and is delayed in its appearance in the blood. At a later period the adrenalin increases in the blood even to the point of hyperadrenal anemia at times. Professor Hata has avoided these untoward effects by divided injections, first giving a small amount of solution, and the remainder one hour and a half later, at which time the adrenalin in the blood had reached its highest level.

But the reaction in this patient was different. It was delayed in onset, and consisted of exacerbation of all the Addisonian features, nausea, vomiting, extreme prostration, decreased blood-pressure and increased pigmentation, and lasted over several

days. It might be likened more to a Herxheimer reaction with an exacerbation of Addisonian rather than syphilitic features. It occurred repeatedly after intravenous arsphenamin injections, but the most marked attack followed an intraspinal treatment. The reaction was prevented by the use of epinephrin.

SUMMARY OF RECENT EXPERIENCES IN THE TREATMENT OF ADDISON'S DISEASE

In the three cases of Addison's disease herein described considerable evidence of improvement was found, comparable in every way to that temporarily induced in the case of Dr. Muirhead. The exacerbation of symptoms in the third case following each arsphenamin injection is of special interest, and particularly the fact that these reactions were largely abolished through the simultaneous administration of epinephrin hypodermically. These four cases on the Muirhead régime reported from this Clinic represent unusually good results. In a more recent chronic case the outcome has been even more gratifying, the patient claiming that his color is entirely normal, and that he feels entirely well. The sixth patient with advanced pigmentation is just beginning to undergo treatment, and the results to date are quite satisfactory.

However, in considering these results we must not be too sanguine. In one chronic case and in three more acute cases of Addison's disease this treatment in our hands has failed absolutely. At best, it is but a form of substitution therapy. The prognosis in Addison's disease is dependent in part at least on the nature and severity of the underlying disease. Thus, in acute Addison's disease secondary to active tuberculosis, little or nothing should be expected from suprarenal therapy since it exercises, in all probability, no influence whatever on the course of the underlying tuberculosis. But in the slowly developing adrenal insufficiency, substitution therapy in the form of the Muirhead treatment offers considerable possibility of both subjective and objective improvement. In the administration of this treatment careful observation is necessary and accurate control of dosage, since epinephrin in excess induces unpleasant

symptoms such as weakness, palpitation, and muscular tremor, while whole gland in excess causes intestinal disturbance and cramps.*

A Study of Pigmentation.—Early in the investigation of these patients it became apparent that the study of color changes was beset with many difficulties, chiefly because in the skin we are dealing not with simple colors, but with mixed or complex colors in which red, blue, and brown participate in varying degrees. Nor are the colors constant over long periods of time. Careful observation discloses the fact that the color of the skin is almost constantly undergoing minor changes in response to heat and cold, to posture, to exercise and rest, to exposure to sunshine, and to vasomotor and nervous influences. The changes incident to exposure to the sunshine have long been fully known and appreciated, but the minor changes incident to these other influences have not received sufficient consideration. It was evident in our experience that a standard of comparison would greatly facilitate studies of color change.

The only feasible method of studying color changes of the skin involved actual reproduction by the artist of the color actually encountered under these varying conditions. Consequently this was undertaken by Miss Bergslund of the Art Department of the Clinic. She has made, from time to time, under constant conditions, exact reproductions of the colors in various areas of the body in ten to twelve cases of Addison's disease. As a result we have accumulated a considerable series of color patches and have been able to analyze, in part, at least, the nature and extent of these color changes.

In determining the effect of the Muirhead régime on the pigmentation it is necessary to make repeated observations of the same skin area and to control, so far as possible, the influences of other factors. For the purpose of studying the pigmentation of the exposed areas of the skin we have selected the middle of the forehead, the neck just below and behind the ear, and the back of the hand; of the unexposed parts, the area of the chest

*A study of the untoward effects encountered in this form of treatment is now being investigated in our wards by Carl H. Greene.

just below the clavicle anteriorly, or in the interscapular space posteriorly.

It soon became quite evident that striking changes in the color of the skin do occur as a result of treatment. In order to determine these changes more readily the various patches of color have been assembled and compared. A tintometer has been developed, with the assistance of Dr. George Brown, consisting of a series of ten patches arranged in a series with increasing amounts of brown, from an arbitrarily selected normal to the deepest brown encountered. The admixture of red is also important, and for very accurate work tintometers have been developed which also take into account the quantitative variations of red. As a result of these investigations we are now utilizing a tintometer representing increasing quantities of brown with an average admixture of red. This has proved very useful in following quantitatively the degrees of pigmentation. The work is still in progress and a detailed description of the instrument will be given later when the color patches have been subjected to quantitative color analysis.*

In concluding, it should be clearly understood that this Clinic deals only in a general way with the early results of treatment of chronic Addison's disease and with the color changes incident to this treatment, and that the treatment itself must be subjected to further trial and over long periods of time before an ultimate decision can be reached relative to its value.

BIBLIOGRAPHY

1. Addison, T.: A collection of the published writings of the late Thomas Addison, physician to Guy's Hospital. London, The New Sydenham Society, 1868, 242 pp.
2. Barker, L. F.: Diseases of the suprarenal glands. Suprarenal insufficiences other than typical Addison's disease. Nelson's Loose-Leaf Medicine, 1920, iii, 220.
3. Muirhead, A. L.: An autograph history of a case of Addison's disease. Jour. Am. Med. Assn., 1921, lxxvi, 652–653.
4. Rowntree, L. G.: Subsequent course of a case of Addison's disease. Jour. Am. Med. Assn., 1922, lxxix, 556–557.

* A colored plate was submitted by the author to show the changes in color, but difficulties of reproduction made it impractical to use it.

THE HEART IN EXOPHTHALMIC GOITER AND ADENOMA WITH HYPERTHYROIDISM

FREDRICK A. WILLIUS
AND
WALTER M. BOOTHBY,
WITH A NOTE ON THE PATHOLOGY BY LOUIS B. WILSON

MUCH of the confusion as to the cause as well as the treatment of the cardiac phenomena of exophthalmic goiter and of adenomatous goiter with hyperthyroidism has been due, first, to an inexact knowledge of the symptoms constituting these diseases which are caused by an improper or increased activity of the thyroid gland, and second, to a failure to differentiate them from more or less similar syndromes, such as cardiac neurosis, irritable heart of soldiers, disordered action of the heart, and neurocirculatory asthenia, which are not attributable to an improper functioning of the thyroid gland.

The details of the differential diagnosis of exophthalmic goiter and adenomatous goiter with hyperthyroidism from each other, and from simulating syndromes, need not be discussed here, but the following definitions of the two diseases will serve to give briefly the concept adopted in this study.

Exophthalmic goiter is a constitutional disease, apparently due to an excessive, probably an abnormal secretion of an enlarged thyroid gland, showing pathologically diffuse, parenchymatous hypertrophy and hyperplasia. It is characterized by an increased basal metabolic rate with the resulting secondary manifestations, with a peculiar nervous syndrome and, usually, exophthalmos, with a tendency to gastro-intestinal crises of vomiting and diarrhea. The cause of the altered pathologic process and activity of the thyroid gland is not known.

Adenomatous goiter with hyperthyroidism is a constitutional

disease, due to the presence in the thyroid gland of adenomatous tissue which, by maintaining an abnormally high and unregulated concentration of thyroxin in the body, causes an increased basal metabolic rate with the resulting secondary manifestations.

METHOD OF STUDY

For the purpose of studying the cardiovascular response in patients suffering from exophthalmic goiter and adenomatous goiter with hyperthyroidism, we have taken a consecutive series of 377 patients on whom electrocardiographic observations were made. Our study covers the out-patient and hospital periods, and includes the complete histories, physical examinations, daily notes, and repeated blood-pressure, pulse-rate, and basal metabolic rate determinations. The electrocardiographic observations were obtained, as a rule, either before or promptly after the patients were admitted to the hospital, also following operative procedures, and prior to dismissal from observation.

In this series of cases exophthalmic goiter was the most common (298 patients, 79 per cent), while adenomatous goiter with hyperthyroidism occurred in only one-fifth of the cases (seventy-nine patients, 21 per cent). Of the patients with exophthalmic goiter eighty-three (28 per cent) were males, and 215 (72 per cent) were females, approximately 1 to 3. Eleven (14 per cent) of the patients with adenomatous goiter with hyperthyroidism were males, sixty-eight (86 per cent) were females, a ratio of 1 to 6.

BLOOD-PRESSURE AND PULSE-RATE

If there is a decrease in the average size of the peripheral cross-section in relation to the rate of blood flow, from a more or less temporary increased resistance of the arteriocapillary muscles, or from a more permanent sclerotic or anatomic condition, both the systolic and diastolic blood-pressure will be proportionately elevated. A high diastolic blood-pressure indicates that the arteries are not relaxed to the normal degree during diastole, and is therefore evidence of an increased resistance in the peripheral arteriocapillary system. Also, if there is

no increase in the average size of the peripheral cross-section when the circulation rate is increased, there will be a distinct rise in systolic pressure with only a slight or moderate rise in the diastolic pressure. If there is a compensatory increase in the average size of the peripheral cross-section, the systolic pressure will be increased to a lesser degree and the diastolic pressure will remain either constant or be somewhat lowered, depending on the magnitude of alteration of the several variants. The increase in metabolism in both exophthalmic goiter and adenomatous goiter with hyperthyroidism means an increased transportation of metabolites to and from the cells, necessitating an increase in circulation rate. Therefore, in cases uncomplicated with primary cardiac disease, or cardiac insufficiency secondary to fatigue, the resulting rapid pulse-rate and heightened pulse pressure is a physiologic manifestation of the response of the circulatory system to bring about this increased rate of circulation.

Table 1

Average blood pressure observations on 377 cases of exophthalmic goiter and adenomatous goiter with hyperthyroidism*

	Out-patient		Entrance		Discharge	
	Exophthalmic goiter	Adenomatous goiter	Exophthalmic goiter	Adenomatous goiter	Exophthalmic goiter	Adenomatous goiter
Systolic	147	153	131	139	128	129
Diastolic	73	83	72	78	75	76
Pulse pressure	74	70	59	61	53	53
Pulse rate	123	110	103	97	96	94

* These figures represent averages of several determinations on many cases and are, therefore, of much greater significance than if they were single observations on individual patients.

There is, in exophthalmic goiter, an elevation in the systolic pressure, while the diastolic pressure is either normal, or more often slightly lowered; it is rarely elevated.[6] The pulse pressure is therefore increased, but in the absence of increased diastolic

pressure, there is no increased peripheral resistance, but rather a relatively dilated periphery to allow the increased rate of circulation with the least cardiac effort. In adenomatous goiter with hyperthyroidism the systolic pressure is considerably elevated, and often to a greater extent than in exophthalmic goiter. Unlike exophthalmic goiter, however, there is on the average an elevation in the diastolic pressure, which in some cases is quite marked, and indicates a relative decrease in the average peripheral cross-section. The pulse pressure, while greater than normal, is usually not as great as in exophthalmic goiter, probably because of a lesser average increase in the metabolism. These facts are most evident when the patient is under stress, as rest in bed modifies but does not obliterate the characteristic blood pressure reactions. Unless some other factor, such as increased peripheral resistance, causes a marked elevation of the diastolic blood-pressure, the pulse pressure in conjunction with the pulse-rate is a quite reliable indication of the circulation rate, and therefore of the basal metabolic rate. If, however, there is a relative increased peripheral resistance, as evidenced by a high diastolic pressure, the pulse pressure is of little value in estimating the circulation rate.

Throughout the consideration on blood-pressure it is to be noted that the observations discussed are averages of numerous determinations on many patients. Slight variations of averages are of far greater significance than variations between individual observations. We wish to emphasize this difference in significance, because observers accustomed to using merely individual readings are apt to consider the variations we emphasize of correspondingly little significance.

The average of the blood-pressure observations made on patients with exophthalmic goiter during the period of out-patient examination were: systolic pressure 147, diastolic pressure 73, pulse pressure 74, and pulse-rate 123. In contrast to these data are the comparable readings on out-patients with adenomatous goiter with hyperthyroidism: systolic pressure 153, diastolic pressure 83, pulse pressure 70, and pulse-rate 110. It is evident that in the latter condition a greater elevation of

both systolic and diastolic pressures occurs, but the most marked difference is in the diastolic.

An analysis of the vasomotor phenomena secondary to the increase in heat production, namely, flushing of the skin and sweating, is usually demonstrable in both conditions, but is more marked and striking in exophthalmic goiter. These phenomena are evidences of dilatation of the peripheral arterioles and capillaries beyond the normal mean, and if taken in conjunction with the foregoing blood-pressure readings indicate that, on the average, there is a greater peripheral dilatation or compensatory relaxation in exophthalmic goiter than in adenomatous goiter with hyperthyroidism. The converse of this is shown by the fact that it is a rare occurrence to find in a case of exophthalmic goiter a diastolic pressure above 90, while in adenomatous goiter with hyperthyroidism it is not unusual to find readings distinctly above 100. The hyperthyroidism from adenomatous goiter is more common toward middle life, and its superposition on a preëxisting idiopathic high blood-pressure (essential vascular hypertension) is sometimes noted. Plummer has suggested that essential vascular hypertension in the presence of adenomatous goiter may favor the development of hyperthyroidism.

As we have noted, blood-pressure reactions in both thyroid disorders are augmented by the patient's activity, in part by increasing the total metabolism, and in part by other strain, probably of a psychic nature. In order to observe the effect of a short period of rest in bed on the average blood-pressure readings, the first two blood-pressure determinations after the patient's admission to the hospital were averaged and compared with the out-patient observations. In exophthalmic goiter the systolic pressure was reduced from 147 to 131; the diastolic pressure remained practically constant (73 and 72); the pulse pressure was diminished from 74 to 59, and the pulse-rate was reduced from 123 to 103. It is of interest that the diminution of pulse pressure is effected by reduction in the systolic pressure, probably resulting from a reduction of the average volume outflow per beat, and from a slowing of the pulse-rate due to a decrease in the total as well as in the basal metabolism. The

diastolic pressure remains essentially constant before and after hospitalization and rest and, therefore, so far as the diastolic pressure can be used to interpret the degree of peripheral arterio-capillary dilatation, this constancy indicates that no further dilatation is produced by rest, and suggests that the peripheral relaxation mentioned as occurring in exophthalmic goiter is practically maximal.

In adenomatous goiter with hyperthyroidism a somewhat different change in blood-pressure observations was noted. The average systolic pressure was reduced from 153 to 139, the diastolic from 83 to 78, the pulse pressure from 70 to 61, and the pulse-rate from 110 to 97. Here again the reduction in pulse pressure results largely from a drop in the systolic pressure. The fall in the average diastolic pressure in adenomatous goiter with hyperthyroidism, although not very great, is distinct, and since we are dealing with averages, suggests that the vascular tree is relatively contracted when under stress, and that there is a tendency toward relaxation as a result of rest. The significance of this average decrease is confirmed by finding frequently a marked decrease in the diastolic blood-pressure following rest, in patients who, primarily, had a distinctly elevated diastolic pressure.

To show the effect of operation and continued rest, the last two blood-pressure readings preceding patients' dismissal from the hospital were averaged. In exophthalmic goiter the average systolic pressure was found to be 128, the diastolic 75, the pulse pressure 53, and the pulse-rate 96. As compared with the previous diastolic pressures, the slight rise following marked improvement in the patient is consistent with the evidence previously cited that, in exophthalmic goiter of marked intensity there is usually relatively dilated vascular periphery. In adenomatous goiter with hyperthyroidism the average systolic pressure was 129, the diastolic 76, the pulse pressure 53, and the pulse-rate 94.

AURICULAR FIBRILLATION

In auricular fibrillation there is an absence of coördinated contraction of the auricular mass with usually a total arhythmia

of the ventricles in which the individual beats vary in strength. When the ventricular rate is rapid a difference often exists between the apical and radial pulse-rate (pulse deficit), because certain ventricular contractions are ineffectual in transmitting an impulse to the more distant vessels, and often even failing to open the aortic cusps.

Auricular fibrillation occurred with about the same degree of frequency in both thyroid disorders. In exophthalmic goiter the incidence was 22 per cent, while in adenomatous goiter with hyperthyroidism it was 24 per cent. For the purpose of analysis and study, the cases of auricular fibrillation have been arbitrarily divided into three groups:

Group 1. Constant Auricular Fibrillation.—In this group are the cases in which the arhythmia was present throughout the period of observation, and includes twenty-three (8 per cent) of the patients with exophthalmic goiter, and eight (10 per cent) of those with adenomatous goiter with hyperthyroidism.

Group 2. Intermittent Auricular Fibrillation.—This group includes those cases in which the arhythmia occurred at irregular intervals of short duration, yet had the tendency to persist throughout the course of observation; it comprised fifteen (5 per cent) of the patients with exophthalmic goiter, and three (4 per cent) of those with adenomatous goiter with hyperthyroidism.

Group 3. Transient Auricular Fibrillation.—In these patients the disorder was present consecutively from one to eight days; it then disappeared and did not recur during our observations. In exophthalmic goiter this incidence was present in twenty-seven (9 per cent), and in adenomatous goiter with hyperthyroidism in eight (10 per cent).

In both thyroid disorders the duration of the disease had been protracted in those patients in whom auricular fibrillation was a constant phenomenon, and, therefore, presumably indicated a more severe degree of cardiac damage. In exophthalmic goiter the average duration of the disease in those patients with this arbitrarily estimated severe type of cardiac damage was sixty-eight months. This average duration of symptoms was

influenced by three cases of ten, fifteen, and seventeen years' intermittent duration, but even exclusive of these, the duration was long. The average duration of illness of patients with the milder, intermittent, or transient auricular fibrillation was definitely shorter, nineteen and twenty months respectively. Patients with adenomatous goiter with hyperthyoridism, who exhibited a constant arhythmia, had had the disease on an average of thirty-one months; those with the intermittent type of auricular fibrillation had had the disease twenty-six months, and patients with transient auricular fibrillation had had the disease ten months. These observations suggest, therefore, that the longer the duration of the disease, the greater the probability of the development of high-grade cardiac damage and resultant fibrillation of the auricles. A shorter duration of the disease in patients with the inconstant types of this arhythmia is a reasonable finding, since less myocardial damage, in general, is to be anticipated.

The intensity of the disease as expressed by the basal metabolic rate, with the consequent increased work required of the cardiac mechanism, was next considered in relation to the development of auricular fibrillation. In exophthalmic goiter associated with the constant type of auricular fibrillation, the average basal metabolic rate was +44 per cent. In the intermittent type the average basal metabolic rate was considerably higher, +61 per cent, while in the transient type it was +45 per cent. In adenomatous goiter with hyperthyroidism with the constant type of arhythmia, the average basal metabolic rate was +33 per cent. In the intermittent and transient type the average values were +44 per cent. These data are somewhat surprising, indicating as they do that the intensity of the disease, as measured by the basal metabolic rate of patients at the time they come under observation, does not in itself greatly influence the severity of the auricular fibrillation, and that the duration of the disease, as we have pointed out, is the more important factor in the development of myocardial damage. In general it would seem that a low-grade or moderate elevation of the basal metabolic rate over a relatively long time may cause greater

damage to the heart than a more marked elevation over a relatively short time.

It is of interest that the average blood-pressure in patients having auricular fibrillation is the same as in those who have a rhythmic cardiac action. In all patients with exophthalmic goiter, and auricular fibrillation, the averages of the blood-pressure readings were systolic 134, diastolic 74, and pulse pressure 60, with a pulse-rate of 100, while patients with the rhythmic cardiac action had a systolic pressure of 133, diastolic 76, pulse pressure 57, and pulse-rate 101. In cases of adenomatous goiter with hyperthyroidism the same relationship was evident. The blood-pressure readings of patients with auricular fibrillation were systolic 138, diastolic 78, pulse pressure 60, and pulse-rate, 100; of patients with rhythmic cardiac action, systolic 137, diastolic 77, pulse pressure 60, and pulse-rate 100. From these data it is evident that alterations in blood-pressure are not a measurable factor in influencing the development of auricular fibrillation in these diseases.

The stress of operation was next considered in its relationship to the production of auricular fibrillation. In exophthalmic goiter, immediately following operative procedures, intermittent or transient auricular fibrillation developed in thirteen (4 per cent) of the patients. In nine instances the disorder followed thyroidectomy, and in four it followed the ligation of a superior thyroid artery. The average duration of auricular fibrillation was one day. Two patients had the auricular fibrillation during the course of acute follicular tonsillitis and it lasted one day. Seven (7 per cent) of the patients with adenomatous goiter with hyperthyroidism had auricular fibrillation following thyroidectomy; the average duration was two days. The development of this disorder following operative procedures does not seem to indicate a particularly dangerous reaction, as none of these patients died; in fact, we have the impression that those patients who have a severe postoperative hyperthyroid reaction are in a safer condition if auricular fibrillation develops than if a very rapid, although regular, rhythm supervenes.

The stress following operative procedures, due in part to the

elevation of the basal metabolic rate, has a marked tendency to bring out auricular fibrillation in hearts with myocardial damage in which evidence of this damage had not been previously discernible. In fact, we have observed several patients who had to have emergency operations of one kind or another develop auricular fibrillation subsequent to the operations; on further study a considerable proportion were found to have had for some time an unrecognized hyperthyroidism of the mild, but long-continued type. The possibility, therefore, of a previously unrecognized hyperthyroidism should always be considered when patients suddenly develop auricular fibrillation under stress. One of us (Willius) has observed a definite relationship between pulse-rate acceleration from work and the production of auricular fibrillation in a case of chronic myocarditis. Acceleration of the pulse-rate to 120 or over as a result of muscular work repeatedly resulted in auricular fibrillation which disappeared when the pulse-rate again dropped below 120. Such a threshold of pulse acceleration was not found in the patients included in this study.

PREMATURE CONTRACTIONS

Premature contractions or extrasystoles are generally conceded to result from increased cardiac irritability. Their presence is not necessarily indicative of organic myocardial damage, as they often occur in normal hearts, and yet the fact must not be overlooked that they may occur with serious cardiac disease. At times the premature contractions are ineffectual and a pulse deficit may result.

In this study premature contractions occurred in forty-three (14 per cent) of the patients with exophthalmic goiter. In twenty-eight of the patients the origin was in the ventricles, in eight in the junctional tissue, and in seven in the auricles. In adenomatous goiter with hyperthyroidism the incidence was about the same, fifteen (15 per cent) of the patients. In ten of these, the origin was in the ventricles, and in five, in the auricles. Premature contractions occurring in both thyroid disorders

have little or no significance, and require no special therapeutic considerations.

SINUS ARHYTHMIA

Sinus, or respiratory arhythmia, is due to phasic slowing and acceleration of the pulse-rate, accompanying respiration, and is due to alterations in vagal tone. Its frequency in children and young adults with normal hearts was first emphasized by Mackenzie. This arhythmia occurred in seven (2 per cent) of the patients with exophthalmic goiter. It was not observed in adenomatous goiter with hyperthyroidism. No significance can be attached to its occurrence in either exophthalmic goiter or in adenomatous goiter with hyperthyroidism.

PAROXYSMAL TACHYCARDIA

Paroxysmal tachycardia is not a common disorder in thyroid disease. Only five (1 per cent) of the patients with exophthalmic goiter developed the condition, and in no instance was it observed in patients with adenomatous goiter with hyperthyroidism. The types of paroxysmal tachycardia were auricular flutter and nodal tachycardia.

Two patients with exophthalmic goiter had auricular flutter. In one patient the flutter tended to persist, and the ventricles were not greatly accelerated, the range being 94 to 150. The auricular rate ranged from 319 to 355. Partial block was present, varying from 2 : 1 to 5 : 1. After the administration of 48 c.c. of tincture of digitalis given in two courses, over a period of eight days, the flutter was converted to a normal rhythm after passing through the intermediate stage of fibrillation. There was no recurrence during the remaining period of observation. The other patient developed a sudden paroxysm of tachycardia about eight hours after ligation of the left superior thyroid vessels; this lasted four days, terminated abruptly, and did not recur. Electrocardiographic examination revealed flutter with 2 : 1 block, the average ventricular rate was 187, and the average auricular rate 375. The highest recorded ventricular rate was 196. Prior to this study we had observed four other cases of auricular flutter in conjunction with exophthalmic goiter.

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NODAL TACHYCARDIA

Paroxysmal nodal tachycardia occurred in three patients with exophthalmic goiter. In each instance it was of the type in which the impulse arose in the middle portion of the node, and was of short duration. No definite therapeutic measures seemed to modify its course, although occasionally vagus pressure terminated the attack suddenly. We have seen no serious outcome resulting from this condition.

DISTURBANCES OF CARDIAC CONDUCTION

Sino-auricular Block.—This condition, or transient standstill of the cardiac mechanism, occurred twice in patients with exophthalmic goiter, and once in patients with adenomatous goiter with hyperthyroidism, and in all instances was transient, and proved of little significance.

Delayed Auriculoventricular Conduction.—One patient with exophthalmic goiter had a delay of impulse transmission between auricles and ventricles (P–R interval 0.28 second), which persisted throughout the period of observation, and was not influenced by atropin. Such a condition, when persistent, must be regarded with concern, as it may predict the development of complete heart-block. Digitalis is contraindicated.

Aberration of the QRS Complexes in All Derivations of the Electrocardiogram.—That the QRS complex of the electrocardiogram occupies the period of conduction of the cardiac impulse through the ventricles has been our contention for a number of years. Recently Wedd and Stroud have also attributed the QRS complex to conduction of the impulse through the ventricles. In those cases in which aberration of the QRS complexes occurs in all derivations, an average high and early cardiac mortality results, a fact noted by Oppenheimer and Rothschild. Willius has repeatedly called attention to the prognostic significance of this electrocardiographic abnormality, and its association with marked degrees of myocardial damage. Two patients with exophthalmic goiter had this disorder. The aberration of the QRS complexes persisted throughout the period of observation. There was no direct evidence that

exophthalmic goiter was the primary cause of the abnormality, as both patients had organic cardiac disease preceding the onset of goiter symptoms. The patients underwent thyroidectomy satisfactorily in spite of the average high mortality attending this cardiac disorder.

SIGNIFICANT T WAVE NEGATIVITY

The T wave in normal electrocardiograms is upright, or positive, in all derivations. By negativity is meant the inversion, or direction downward, of the wave. Willius, in several publications, has called attention to certain facts regarding T wave negativity: (1) That T wave negativity in Derivation III alone occurs very often in normal hearts, and that no prognostic significance can be attached to this, (2) that T wave negativity in Derivation II alone and in combined Derivations I and III does not occur, and (3) that the following T wave negativities have marked prognostic significance, provided the negativity is independent of digitalis in the following order of importance: T wave negativity in combined Derivations I and II, in Derivation I alone, in combined Derivations I, II, and III, and in combined Derivations II and III. Another idea was presented in associating these graphic findings with obliterative intrinsic vascular disease. Evidence substantiating this belief is constantly accumulating, but cannot be dealt with in this discussion.

In exophthalmic goiter significant T wave negativity occurred in only three instances (1 per cent). In one case the T wave negativity occurred in combined Derivations I and II, and in two cases in all derivations. In adenomatous goiter with hyperthyroidism significant T wave negativity occurred in two (2 per cent) cases. In one patient the T wave negativity occurred in Derivation I alone, and in the other in combined Derivations I and II.

The extreme infrequency of significant T wave negativity in both thyroid disorders is further confirmatory evidence in favor of the conception of Willius of the relationship of obliterative intrinsic vascular disease to its production. Important

degenerative cardiac changes in exophthalmic goiter and in adenomatous goiter with hyperthyroidism are not common; however, when they do occur, they are apparently limited to the myocardium; the vascular structure and, therefore, the blood supply and nutrition remain uninvolved.

P WAVE NEGATIVITY IN DERIVATION III

Not infrequently the P wave in Derivation III is found to be transiently negative, and occasionally this negativity is persistent. The reasons for this observation are not fully understood. Twenty (7 per cent) of the patients with exophthalmic goiter had P wave negativity in Derivation III. In only two instances was the negativity persistent. In the eighteen variable instances it occurred during the course of digitalis administration in nine. Ten (13 per cent) of the patients with adenomatous goiter with hyperthyroidism had P wave negativity in Derivation III. The persistent type occurred in one, while in nine the negativity was transient, occurring in four instances during treatment with digitalis. No definite conclusions can be drawn regarding the significance of P wave negativity in Derivation III.

CARDIAC EFFICIENCY

The constant elevation of the basal metabolic rate and the total metabolism in exophthalmic goiter and in adenomatous goiter with hyperthyroidism necessitates an increased circulation rate, and a greater utilization of a unit quantity of blood. The former is accomplished in two ways: by increase in number of beats each minute, and by increase in the volume output of each beat. There is no practical method for estimating the volume for each beat. On account of the many extraneous factors that influence the heart rate, the latter is only a very rough index of the increased work thrown on the heart. Increased cardiac work theoretically leads to hypertrophy of the myocardium, chiefly affecting the left ventricle. Myocardial hypertrophy and dilatation are usually coincident events and the dominance of the former largely determines the efficiency

of the circulation. The forcible tumultuous cardiac action results from acceleration of rate, and increased force of contraction, both phenomena being in greater part the expression of elevated metabolism, to which they are due.

However, in exophthalmic goiter the tumultuous character of the heart beat is more marked for a given increase in the basal metabolic rate than in adenomatous goiter with hyperthyroidism, or in leukemia with a correspondingly increased metabolism. This suggests the possibility of an intangible effect on the cardiac irritability resulting from the local increased oxidation and intoxication from the excess of thyroxin, and, in the case of exophthalmic goiter, the irritability may be enhanced by the alteration in the composition of the thyroxin molecule. Plummer and Boothby have shown that patients with moderately severe exophthalmic goiter are very inefficient in converting potential energy into any kind of motion as, in walking on a treadmill, they require approximately twice as many net gram calories for each horizontal kilogram-meter as normal persons. If the voluntary striated muscular system is inefficient, it seems reasonable that the same intoxication would cause a similar degree of inefficiency in the cardiac musculature. This inefficiency, with the increased output demanded of the heart in its apparently hyperirritable condition, probably accounts for the tumultuous type of excessive cardiac action and the rather frequent occurrence of cardiac decompensation, particularly in cases of long duration.

CARDIAC MURMURS

Cardiac murmurs are common in both thyroid diseases. They were present in exophthalmic goiter in 121 (41 per cent) of the patients, and in adenomatous goiter with hyperthyroidism in forty (51 per cent). In only two instances in the group were the murmurs due to endocardial valvular diseases. The murmurs not of endocardial origin were of two types, both systolic in time, and blowing in quality; the first has its point of maximal intensity at the third left intercostal space and is usually quite localized; the second is best heard at the apex and has frequently a variable transmission. Both murmurs may be present.

The murmur heard at the third left intercostal space is evidently functional in origin, possibly associated with changes in the blood flow, and disappears with a slowing of the circulation rate as the disease is arrested. The apical systolic murmur is probably due to regurgitation at the mitral valve due to dilatation of the left ventricle. The murmur has likewise invariably disappeared in our cases with the termination of the disease. These murmurs are not indicative of the presence of cardiac damage in the sense of a primary valvular lesion.

The auscultatory findings in the hearts of both exophthalmic goiter and adenomatous goiter with hyperthyroidism are often confused with those of endocardial valvular disease. The diagnosis of mitral stenosis is the most common error made, as the apical systolic murmur is at times prolonged, often rough and reverberant, and if examination is hasty, may give the impression of being presystolic in time. The tumultuous type of cardiac action completes the false evidence giving rise to this error.

The peripheral arteriole and capillary dilatation in exophthalmic goiter may cause a capillary pulse, and thus lead to an erroneous diagnosis of aortic regurgitation. Needless to say, this error is inexcusable, as the assumption of the presence of aortic regurgitation is never justifiable in the absence of a diastolic murmur.

CARDIAC ENLARGEMENT

The hearts of most of the patients with exophthalmic goiter or adenomatous goiter with hyperthyroidism were only moderately enlarged; the left border, as a rule, was 1.5 to 2 cm. beyond the usual normal limit of cardiac dulness. Extreme cardiac enlargement occurring in patients with marked cardiac disease will be discussed later.

EDEMA

Slight to moderate edema of the lower extremities is evident in about one-fifth of the patients at the time of admission to the hospital; a few had marked edema with peritoneal and pleuritic

effusion. Edema occurred in 21 per cent of the patients with exophthalmic goiter, and in 20 per cent of the patients with adenomatous goiter with hyperthyroidism, and persisted on the average for three days after hospitalization. Complete rest in bed usually resulted in the disappearance of the edema except in cases of cardiac disorders.

SEVERE CARDIAC DAMAGE

As we have mentioned, severe cardiac damage is less common in cases of exophthalmic goiter and adenomatous goiter with hyperthyroidism than is generally believed. When present, however, it forms a very dominant factor in the prognosis and treatment; therefore the cases in this series in which there was severe cardiac damage are reported in detail.

Seven Cases of Exophthalmic Goiter and Severe Cardiac Disease

Case 1 (A361513). H. E. S., a man, aged forty-two years, had edema, extending to the waist, but there was no free fluid in the serous cavities. Cardiac dulness extended 3.5 cm. to the right and 15 cm. to the left of the midsternal line. No murmurs were audible. Total arhythmia of auricular fibrillation was present throughout the period of observation. The edema disappeared after seven days of complete rest in bed and the administration of digitalis. Three courses of digitalis were given: 32, 18, and 15 c.c. over a period of six, three, and four days, respectively, at intervals of twenty-one and thirteen days. Thyroidectomy was performed without incident, and the patient recovered satisfactorily. The average preoperative basal metabolic rate was +67 per cent.

Case 2 (A373496). J. W. B., a woman, aged forty-eight years, had moderate edema of the lower extremities, dyspnea, orthopnea, and moderate cyanosis. The cardiac dulness extended 5 cm. to the right and 17 cm. to the left of the midsternal line. The auricles fibrillated throughout the period of observation. No murmurs were audible. The edema persisted eight days. Two courses of digitalis, 14 and 7 c.c., were given over periods of three days each, at an interval of four days. Thyroidectomy was performed without complications, and convalescence was normal. The average preoperative basal metabolic rate was +29 per cent.

Case 3 (A386647). O. H. R., a woman, aged forty-four years, had moderate edema of the lower extremities with marked dyspnea and moderate cyanosis. Cardiac dulness extended 4 cm. to the right and 12 cm. to the left of the midsternal line. Auricular fibrillation was persistent, but no murmurs were heard. The edema lasted seven days. Three courses of digitalis were administered: 20, 24, and 6 c.c. over periods of four, five, and two days respectively, at intervals of sixty-one and fifteen days. The edema

disappeared and cardiac compensation at rest was restored. Ligation of the superior thyroid vessels was accomplished without incident. The patient returned recently for observation with the heart again decompensated, and marked anasarca and cardiac therapy is still in progress. The preoperative basal metabolic rate was +83 per cent.

Case 4 (A381283). G. A. M., a man, aged fifty-six years, had moderate edema of the lower extremities, dyspnea, and moderate cyanosis. The cardiac dulness extended 3 cm. to the right and 10 cm. to the left of the midsternal line. The auricles were fibrillating throughout the period of observation. The edema persisted for five days. Compensation was restored by giving two courses of digitalis of 21 and 12 c.c. over periods of five and three days, with an interval of twenty days. Thyroidectomy was performed after one superior ligation and the convalescence was uneventful. The average preoperative basal metabolic rate was +62 per cent.

Case 5 (A366388). H. G. B., a man, aged fifty-one years, had dyspnea, moderate cyanosis, and general anasarca. The cardiac dulness extended 3 cm. to the right and 11 cm. to the left of the midsternal line. Auricular fibrillation was persistent, and a systolic apical murmur was heard. The edema did not completely disappear for fifteen days. Three courses of digitalis were administered: 20, 19, and 10 c.c. were given over periods of three, seven, and four days at intervals of twenty and twenty-five days. Thyroidectomy was performed, and convalescence was satisfactory. The average preoperative basal metabolic rate was +54 per cent.

Case 6 (A832). F. A., a woman, aged fifty-eight years, had marked dyspnea, moderate cyanosis, and moderate edema of the lower extremities. The cardiac dulness extended 4 cm. to the right and 20 cm. to the left of the midsternal line. A rough blowing apical systolic murmur was heard, and the auricles were persistently fibrillating. The edema lasted thirteen days and showed a tendency to recur, even with complete rest in bed. Three courses of digitalis were given, of 20, 14, and 15 c.c., over periods of four, three, and four days, at intervals of nine and eight days. Operative procedures were not advised in this case. The average basal metabolic rate was +22 per cent.

Case 7 (A361242). F. M. H., a woman, aged fifty-two years, had dyspnea, moderate cyanosis, and moderate edema of the lower extremities. The cardiac dulness extended 4 cm. to the right and 13.5 cm. to the left of the midsternal line. Auricular fibrillation was persistent. The edema lasted seven days. Four courses of digitalis were given of 15, 5, 7, and 4 c.c. each, over periods of four, two, three, and two days, at intervals of two, fourteen, and fifteen days. Thyroidectomy resulted in an uneventful recovery. The average preoperative basal metabolic rate was +47 per cent.

Two Cases of Adenomatous Goiter With Hyperthyroidism Complicated by Severe Cardiac Damage

Case 8 (A390439). M. C. G., a man, aged forty-four years, had marked dyspnea, moderate cyanosis, and edema of the lower extremities. The cardiac dulness extended 6 cm. to the right and 12 cm. to the left of the midsternal line. Auricular fibrillation was persistent, and an apical systolic

murmur was audible. The edema lasted six days. Three courses of digitalis were administered, of 12, 17, and 14 c.c. each, over periods of three, six, and three days, at intervals of seventeen and four days. This was followed by thyroidectomy without incident. The average preoperative basal metabolic rate was +39 per cent.

Case 9 (A380271). W. H. S., a man, aged sixty-two years, had marked dyspnea, and slight edema of the extremities. The cardiac dulness extended 5 cm. to the right and 12 cm. to the left of the midsternal line. Auricular fibrillation was persistent, and a systolic apical murmur was transmitted into the axilla. Two courses of digitalis were given, of 11 and 7 c.c. each, over periods of four and three days respectively, with an interval of fourteen days. Thyroidectomy was performed without incident. The average preoperative basal metabolic rate was +15 per cent.

It should be noted that in this series none of the patients with severe cardiac disease died, in no instance was an alarming postoperative reaction noted, and in only one instance was operation considered inadvisable on account of the cardiac condition.

THE VALUE OF DIGITALIS

Certain recent publications would indicate that erroneous impressions exist with regard to the value of digitalis in myocardial disease complicating exophthalmic goiter or adenomatous goiter with hyperthyroidism. This is contrary to our experience, as we daily observe marked beneficial effects following the administration of this drug. Our observations are based entirely on the Minnesota-grown digitalis leaf, purpurea, prepared as a tincture, and standardized according to the Hatcher cat-unit method. Digitalis was administered to 105 (35 per cent) of the patients with exophthalmic goiter and to forty (41 per cent) of those with adenomatous goiter with hyperthyroidism. The average amount of digitalis given to each patient was 17 c.c. in one course of four days. In other cases more than one course was given. A slowing of the pulse-rate was noted in both thyroid disorders. In cases of exophthalmic goiter the average decrease was four beats each minute, while in adenomatous goiter with hyperthyroidism it was fifteen beats each minute. A slight elevation in pulse pressure was evident, from 62 to 65 in exophthalmic goiter, and from 59 to 65 in adenomatous goiter with hyperthyroidism.

Cohn, Fraser, and Jamieson have shown that negativity of the T wave developed in the electrocardiogram during and following the administration of digitalis. In this study this graphic effect of digitalis was often observed, occurring in forty-one (39 per cent) of the patients with exophthalmic goiter to whom the drug was administered, and in fourteen (34 per cent) of the patients with adenomatous goiter with hyperthyroidism who received the drug. The negativity usually affected combined Derivations II and III and combined Derivations I, II and III, and was transient and variable.

In only five cases, all occurring in the exophthalmic goiter group, were prolongations noted of an auriculoventricular conduction time beyond normal (P–R 0.24 to 0.28 second).

Our observations on the drop in pulse-rate, elevation of pulse pressure, and production of T-wave negativity demonstrate that digitalis in both exophthalmic goiter and in adenomatous goiter with hyperthyroidism has a definite effect; that this effect was beneficial was evidenced by the general clinical and cardiac improvement in the patients.

Even in the absence of symptoms of cardiac decompensation we often consider it advisable to digitalize the patient before operation, so that if cardiac failure supervenes, further administration of the drug may be instituted without loss of time. We are in accord with Christian's view that digitalis is of distinct value in rhythmic cases with cardiac decompensation as well as in those exhibiting auricular fibrillation. Of course, influence on the increase in pulse-rate, secondary to the increased metabolism, is not to be expected; the increase, however, due to cardiac insufficiency and superimposed on the former is as markedly affected as in other diseases.

Our usual method of administration is in three doses daily of 2 c.c. of the tincture, until a total of 16 to 18 c.c. has been given, an effort being made to discontinue the digitalis before nausea develops. According to the individual indications, after a few days' intermission subsequent courses of digitalis may be given.

OPERATIVE PROCEDURES

The operative procedures in the cases of exophthalmic goiter in this study were, primary thyroidectomy in 121 (41 per cent) cases, preliminary measures such as hot water injections and ligation of vessels, followed by thyroidectomy in 135 (45 per cent) cases, and preliminary procedures as yet not followed by thyroidectomy in thirty-eight (13 per cent) cases. Four (1 per cent) of the patients were not operated on. Primary thyroidectomy was performed on seventy (89 per cent) of the patients with adenomatous goiter with hyperthyroidism, and thyroidectomy preceded by preliminary measures in seven (9 per cent). Two patients (2 per cent) were not operated on.

FACTORS IN THE CAUSATION OF DEATH

The opinion is prevalent among surgeons and clinicians that many deaths occurring in cases of exophthalmic goiter and adenomatous goiter with hyperthyroidism are due to heart failure. This has not been our experience, as is shown by the following review of the salient points in the case histories of the patients in this series who died.

PATIENTS WITH EXOPHTHALMIC GOITER WHO DIED

Case 10 (A362244). E. W., a woman, aged twenty-four years, died twenty-four hours after ligation of the right inferior thyroid vessels. The clinical picture was that of a fulminating type of influenzal bronchopneumonia. The heart showed no evidence of failure, and death occurred following respiratory failure from the marked involvement of the lung. Necropsy was not permitted.

Case 11 (A372930). M. G., a woman, aged twenty years, died forty-eight days after thyroidectomy from septicemia. Necropsy revealed splenitis with infarction and multiple abscess formation, acute serofibrinopurulent left pleuritis, and acute diffuse nephritis. There was no evidence of heart failure during the clinical course, and no appreciable cardiac changes were found at necropsy.

Case 12 (A388765). F. M., a man, aged fifty-nine years, died of visceral degeneration due in part to the prolonged course of the exophthalmic goiter syndrome, and in part to a superimposed secondary infection. No operation was performed. Jaundice was marked; nausea and vomiting, intermittent fever, and finally thrombophlebitis of the right leg developed, and death resulted from gradual inanition. Necropsy disclosed marked, destructive hepatitis, acute putrefactive seropurulent right pleuritis, moderate myocardial

degeneration, thrombosis of the right femoral vein, acute toxic nephritis of jaundice, and marked dilatation of the gall-bladder. There was nothing in this case to indicate a cardiac death.

Case 13 (A382100). F. A., a woman, aged fifty years, died of visceral degeneration, due in part to the prolonged course of the exophthalmic goiter syndrome, and in part to the superposition of a secondary infection. The clinical course of the disease was similar to that of the preceding case, with the exception of thrombophlebitis. No operative procedures were undertaken. Necropsy revealed chronic pancreatitis, right hydrothorax, old healed fibrous pleuritis, peritonitis, chronic cholecystitis, and cholelithiasis.

Case 14 (A380262). C. J., a man, aged sixty-eight years, died six days after ligation of the right inferior thyroid vessels from embolic gangrene of the left leg. Necropsy revealed advanced arteriosclerosis, gangrene of the left leg, infarction of both kidneys, hypertrophy of the heart with fibrosis, and a ball thrombus and mural thrombosis of the left auricle.

Case 15 (A371306). G. G., a man, aged sixty-four years, died of respiratory obstruction seven days after thyroidectomy. A tracheotomy was performed soon after the operation, but the patient developed purulent bronchitis and pneumonia, and died. Necropsy disclosed septic bronchitis, bilateral gangrenous pneumonia, and mediastinitis. There was moderate cardiac dilatation and hypertrophy.

Case 16 (A381275). H. W., a woman, aged forty-six years, died twenty-four hours after the injection of 1 c.c. of boiling water into the thyroid gland. The clinical syndrome was that of so-called acute hyperthyroidism, with no cardiac signs other than tachycardia and dyspnea. The syndrome suggested, but was not typical of, pulmonary embolism. At necropsy only questionable dilatation and hypertrophy of the heart were noted. There was a moderate degree of diffuse nephritis.

PATIENTS WITH ADENOMATOUS GOITER WHO DIED

Case 17 (A385692). J. W., a woman, aged forty-five years, died four days after thyroidectomy from respiratory obstruction. At necropsy edema of the glottis with respiratory obstruction was found. There was moderate cardiac hypertrophy with fibrous degeneration.

Case 18 (A390564). W. F., a man, aged forty-seven years, had well-advanced acromegaly besides hyperthyroidism from adenomatous goiter. He died seven days after thyroidectomy from purulent bronchitis and pneumonia, subsequent to tracheotomy. Necropsy disclosed bilateral bronchopneumonia, acute pleuritis, pituitary tumor, and acromegaly.

Case 19 (A394308). F. F., a woman, aged fifty-two years, died six days after thyroidectomy from typical uremia with a sudden rise in the blood urea to 144 mg. for each 100 c.c. At necropsy extreme inflammation and hypoplasia of both kidneys and suppurative ulcerative colitis and marked arteriosclerosis were found.

We thought it advisable to enlarge our study by reviewing all the deaths that occurred in both thyroid diseases during a

period of six months preceding and six months following the study.

In these additional cases of exophthalmic goiter the deaths resulted from respiratory obstruction due to edema of the glottis one day after thyroidectomy (Case 20); acute rheumatic fever, acute endocarditis and pneumonia, no operation (Case 21); lobar pneumonia and acute vegetative endocarditis, no operation (Case 22); acute thyroid crisis twenty-four hours after subcutaneous injection of 1 c.c. of 0.5 per cent novocain (Case 23); acute thyroid crisis with manifestations in the central nervous system, no operation (Case 24); inanition from thyroid crisis eighteen days after ligation of the left superior thyroid vessels (Case 25); acute thyroid crisis with manifestations in the central nervous system, no operation (Case 26), and sudden death in the operating-room before any procedures were undertaken (Case 27).

In the additional cases of adenomatous goiter with hyperthyroidism the deaths resulted from pneumonia and respiratory difficulty two days after thyroidectomy (Case 28); respiratory obstruction due to edema of the glottis one day after thyroidectomy (Case 29); hyperthyroidism with dementia two days after thyroidectomy (Case 30); acute hyperthyroidism with dementia two days after thyroidectomy (Case 31), and myocardial degeneration with bronchopneumonia, no operation (Case 32).

Without question fourteen (Cases 10, 11, 12, 13, 14, 15, 17, 18, 19, 20, 21, 22, 28, and 29) of the twenty-three deaths can in no way be considered cardiac in origin. The other cases, however, need further discussion.

Cases 16 and 23 presented a characteristic terminal syndrome, consisting of progressive acceleration of the heart rate, accompanied by tumultuous cardiac action, shallow and rapid respiration, with cyanosis in the later stages. The metabolism was not measured in these cases after the onset of the crisis, but indications were those of a marked increase in the basal metabolic rate, which, however, was probably not the causative factor of this syndrome. The peculiar reaction responsible for this is

not clear, and may be suddenly and unexpectedly precipitated. Even with the most careful search for factors indicating the likelihood of development of this syndrome, few that were tangible were found until Plummer's recent discovery that in all probability it is due to an incompletely iodized thyroid secretion. Many observers have erroneously believed this reaction to be of primary cardiac origin. The time-worn statement that such deaths are due to heart failure has been a convenient cloak for surgeons and clinicians, and has resulted from a failure of critical analysis of prelethal symptoms and signs, and necropsy findings. At necropsy insufficient evidence is disclosed to ascribe death to cardiac causes. Although in most cases degenerative myocardial changes were found, they could not be considered the dominant factor producing death.

Cases 24, 25, 26, 30, and 31 presented the same cardiovascular phenomena as noted in Cases 16 and 23, with disturbances of the central nervous system, and also with marked irritability, dementia, or coma. The most tangible preoperative evidence of a threatening catastrophe seems to be the warning given by the presence of undue irritability or stimulation, alternating with, or dominated by, a despondent attitude.

Here, again, the clinical course before death, and the necropsy findings fail to disclose evidence sufficient to convict the heart of being the primary cause of death.

In this same type of case, two patients, one of whom is included in this series (Case 24) were followed through the period of death with electrocardiographic study over periods of six and fourteen hours respectively. In both instances a normal cardiac mechanism was maintained until a few minutes before death, when the graphic phenomena of cardiac asphyxia became evident.

The suddenness of the death in Case 27 in the operating-room, before operative procedures were undertaken except laying the patient on the table, warrants discussion as to the possibility of death being primarily cardiac. This patient had been assigned for operation reluctantly because of possible organic degenerative changes, due to long duration of the disease (sixteen intermittent years), and to weakness and loss of appetite, but there

was nothing outstanding regarding the cardiac condition. This patient already had had two partial thyroidectomies. At necropsy a marked general lymphoid hyperplasia was found, conforming to the findings of so-called status lymphaticus, commonly associated with sudden inexplicable death. The heart showed a moderate degree of hypertrophy and dilatation; otherwise the findings were negative.

Case 32 (adenomatous goiter with hyperthyroidism) represents the only death in this group that we believe can justly be considered of primarily cardiac origin. The patient had general anasarca, was dyspneic and cyanotic, the heart was markedly enlarged and the auricles persistently fibrillated. Operation was not advised. Necropsy revealed marked hypertrophy and dilatation of the left ventricle.

The deaths in cases 21 and 22 were from acute endocarditis, which, in its relationship to hyperthyroidism, must be considered a distinct and separate disease.

POSTOPERATIVE ANOXEMIA

Patients who, subsequent to operation, become dyspneic, cyanotic, hoarse, and develop dysphagia with nasal regurgitation of fluids, usually accompanied by an increased heart rate, are sometimes considered as dying from heart failure, especially if the symptoms of respiratory obstruction are only slight (Cases 15, 17, 18, 28, 29). Careful clinical differentiation reveals that the cardiac phenomena of anoxemia are in the main due to this condition which, although often of slight degree, has continued for considerable time. Asher has demonstrated that animals rendered hyperthyroid by feeding thyroid extract are extremely sensitive to even a slight decrease in the concentration of the oxygen in the inspired air. Partial laryngeal obstruction resulting from injury to the recurrent laryngeal nerve is probably the most common cause of anoxemia. However, we have seen one case in which there was definite postmortem evidence that an enlarged thymus with slight edema and hemorrhage in the anterior mediastinum probably interfered with the free return of blood to the right auricle.

GENERAL DISCUSSION AND SUMMARY

From a study of the data presented in this paper the most outstanding fact is the infrequency in both exophthalmic goiter and adenoma with hyperthyroidism of symptoms indicating cardiac disease: only one-fourth of the patients had auricular fibrillation, and in less than one-half of these was the fibrillation a constant phenomenon; about one-fifth had, as evidence of slight cardiac weakness, a moderate degree of edema of the legs which disappeared readily under treatment with rest and digitalis. Not more than 2 per cent of the patients had sufficient clinical evidences of myocardial injury to classify them as having serious cardiac disease. When serious cardiac damage is present, however, it is a very dominant factor in prognosis and treatment. In this limited group operative mortality can be greatly reduced by measures directed to the restoration and maintenance of cardiac compensation. The misconception of the frequency in hyperthyroidism of cardiac disease undoubtedly arose from interpreting the increased heart rate as evidence of a pathologic condition of the heart, whereas it is evidence of its normal response to the increased demand made on it, until the later stages, when the symptom is supplemented by those of fatigue with auricular fibrillation.

The opinion is prevalent that many of the deaths in both diseases are due to heart failure as the major factor. Death is a complex process. It is difficult to estimate the relative importance of the various factors involved, but we believe that our data permit us to do so with more clearness and exactness than heretofore, and possibly to eliminate some misunderstandings on the subject.

Our experience has been that these patients, if they have received appropriate cardiac treatment, apparently do not die of heart failure. In a consecutive series of twenty-three deaths, including postoperative deaths as well as deaths before operative intervention was possible, there was only one in which the heart could be considered as the major contributory cause. This patient had general anasarca, was dyspneic and cyanotic, the heart was markedly enlarged, and the auricles persistently fibril-

lated throughout the period of observation; at no time was operative intervention considered.

Deaths from a postoperative acute hyperthyroid crisis with increasing elevation of the heart rate, with or without the development of auricular fibrillation, have, as a rule, been considered by the surgeon as due to heart failure. A careful analysis of the symptoms in our series of cases reveals that such an interpretation of death is not in the main justified except for the final cataclysm. The evidence points to the reverse conclusion, because the increased heart rate is an expression of the attempt of the heart to increase its volume output sufficiently to meet the demands made on it by the greatly increased metabolism. It is undoubtedly true that the heart muscle, like other tissues in the body, is rendered more irritable and less efficient by the intense thyroid intoxication.

This cardiac reaction closely simulates, although in an exaggerated form, the symptoms seen during the height of a severe acute infection. Because the postoperative hyperthyroid crisis is more prone to occur in patients with a high degree of hyperthyroidism, especially when associated with the irritability, mental instability and depression characteristic of exophthalmic goiter, and because the intensity of the reaction and the number of deaths are decreased by the administration of iodin, as shown by Plummer's recent investigation, it is probable that the reaction is dependent on a peculiar intoxication caused by the presence in the body of an excess of an incompletely iodized thyroid secretion. The intensity of this reaction varies greatly; certain patients barely survive; others might survive provided the heart could withstand the strain even twenty-four hours longer; in this latter sense the condition of the heart must, of course, be considered as a contributory factor.

From the study of the various data, and from an analysis of the individual case reports, especially of patients who died, the conclusion is evident that, if the patient is properly treated, cardiac death in exophthalmic goiter and in adenomatous goiter with hyperthyroidism is a very rare occurrence. The finding at necropsy of fatty degeneration of the heart, which in some

cases is no more than that found in persons who die of old age, appears to us an expression of the effect of a long-continued or intense toxemia, combined with increased activity. Similar changes have been reported in certain voluntary muscles like the quadriceps, and therefore the fatty degeneration of the heart cannot be regarded as the major cause of death, although if extreme it may render the heart unable to withstand the strain until the crisis is past.

The question of surgical mortality in cases of exophthalmic goiter, and in those of adenomatous goiter with hyperthyroidism, is an expression of the detailed care and coördination of the medical, laboratory, and surgical services. Patients with these diseases are very susceptible to anoxemia, and consequently injury to the recurrent laryngeal nerves and the production of laryngeal edema are particularly dangerous, as they place a still greater load on the already overloaded heart. For the avoidance of these as well as other surgical dangers in the maintenance of a low surgical mortality, the major portion of the credit justly belongs to the surgeon. On the other hand, as we have emphasized, the hearts of patients with exophthalmic goiter, and adenomatous goiter with hyperthyroidism, are subjected to tremendous demands, demands far in excess of those made in any other disease; in consequence it is incumbent on the physician and the surgeon to aid the heart by appropriate measures of treatment. If such measures are instituted, the evidence indicates that the intensity and character of the toxemia and not the condition of the heart are the major factors in producing death.

NOTE ON THE PATHOLOGY OF THE HEARTS AND THE CASES DESCRIBED IN THE SERIES

The hearts from the cases on which the foregoing clinical report is based are a small group in a large series, the pathology of which I am at present studying. Although the group considered alone is too small and the patients concerned represent too wide a variation in age, continuation, and type of disease

to warrant conclusions from the pathologic data alone, yet the following results of their review may be of interest.

Of the hearts of the twenty-one cases which came to necropsy some degree of hypertrophy was noted in sixteen. This was marked in two instances in which the heart weighed 500 and 550 gm. respectively. The hearts were both in large females, one with exophthalmic goiter, and the other with nodular goiter, associated with an acute terminal fibrinous pericarditis. The hypertrophy in the other instances was from 5 to 10 per cent increase in weight. In two of the hypertrophied hearts fibrosis was present.

Eleven of the sixteen patients with hypertrophied hearts were past forty-five years of age. One was fifteen, one thirty-five, and one thirty-eight years. Ten of the sixteen hypertrophied hearts revealed unquestioned dilatation as well as hypertrophy.

No note appears in the necropsy findings concerning dilatation or hypertrophy of the heart in the other five cases except that in one the heart is noted as weighing 250 gm. and being "firm and beefy" in texture. As is usual in exophthalmic goiter the hearts at necropsy were mostly pale, soft, and somewhat dilated.

Histologically, the myocardium of eighteen of the patients shows apparently swollen fibers with indistinct striations and well-marked lipoid changes. However, only five of the patients from whom hearts were examined were under forty years of age. It is difficult, therefore, accurately to determine whether the lipoid changes were greater than might have been expected in persons more than forty years of age without exophthalmic goiter. It is apparently true, however, that in persons with long-continued, pronounced hyperthyroidism the myocardium reveals more advanced fat changes than are present in the myocardium of persons of the same age without hyperthyroidism.

The pathologist's impression of these hearts, both grossly and microscopically, is that of weak rather than strong muscles, although, as it appears from this series of cases, a large proportion of the hearts show muscular hypertrophy.

BIBLIOGRAPHY

1. Asher, L., and Duran, M.: Beiträge zur Physiologie der Drüsen. Das Verhalten von normalen, mit Schilddrüsensubstanz gefütterten und Schilddrüsenlosen Ralten gegen Sauerstoffmangel. Biochem. Ztschr., 1920, cvi, 254–274.
2. Blackford, J. M., and Willius, F. A.: Auricular flutter. Arch. Int. Med., 1918, xxi, 147–165.
3. Boothby, W. M.: The fundamental classification of disease by the basal metabolic rate. Jour. Am. Med. Assn., 1921, lxxvi, 84–86.
4. Boothby, W. M.: The basal metabolic rate in hyperthyroidism. Jour. Am. Med. Assn., 1921, lxxvii, 252–255.
5. Boothby, W. M., and Sandiford, I.: A laboratory manual of the technic of basal metabolic rate determinations. Philadelphia, W. B. Saunders Co., 1920, 117 pp.
6. Boothby, W. M., and Sandiford, I.: I. A preliminary note on the food requirement in hyperthyroidism. II. A comparison of hyperthyroidism in men and in women. Med. Clin, N. Amer., Philadelphia, 1921, v, 425–438.
7. Christian, H. A.: Digitalis therapy: satisfactory effects in cardiac cases with regular pulse-rate. Am. Jour. Med. Sc., 1919, clvii, 593–602.
8. Christian, H. A.: Essential vascular hypertension. Oxford Medicine, 1921, iii, 751–766.
9. Cohn, A. E., Fraser, F. B., and Jamieson, R. A.: The influence of digitalis on the T wave of the human electrocardiogram. Jour. Exper. Med., 1915, xxi, 593–604.
10. DuBois, E. F.: Metabolism in exophthalmic goiter. Arch. Int. Med., 1915–1916, xvii, 915–964.
11. Goodpasture, E. W.: Myocardial necrosis in hyperthyroidism. Jour. Am. Med. Assn., 1921, lxxvi, 1545–1551.
12. Goodpasture, E. W.: The influence of thyroid products on the production of myocardial necrosis. Jour. Exper. Med., 1921, xxxiv, 407–423.
13. Greenfield, W. S.: Some diseases of the thyroid gland. Lancet, 1893, ii, 1493–1497.
14. Hamilton, B. E.: Clinical notes on hearts in hyperthyroidism. Boston Med. and Surg. Jour., 1922, clxxxvi, 216–218.
15. Hamilton, B. E., and Lahey, F. H.: Differentiation of hyperthyroidism and of heart disease from neurasthenic states. Jour. Am. Med. Assn., 1922, lxxviii, 1793–1796.
16. Kendall, E. C.: The isolation in crystalline form of the compound containing iodin which occurs in the thyroid; its chemical nature and physiologic activity. Collected Papers, Mayo Clinic, 1915, vii, 393–421; Jour. Am. Med. Assn., 1915, lxiv, 2042–2043.
17. Kendall, E. C.: The active constituent of the thyroid: its isolation, chemical nature, and physiologic action. Collected Papers, Mayo Clinic, 1916, viii, 513–527.
18. Kendall, E. C.: The physiologic action of thyroxin. Collected Papers, Mayo Clinic, 1919, xi, 417–423.
19. Mackenzie, J.: Disease of the heart. London, Frowde, 1914, 183–188.

20. Magnus-Levy, A.: Ueber den respiratorischen Garwechsel unter dem Einfluss der Thyreoidea, sowie unter verschiedenen pathologische Zuständen. Berl. klin, Wchnschr., 1895, xxxii, 650–652.
21. Mayo, C. H., and Boothby, W. M.: The mortality rate following operations on the thyroid gland. Jour. Am. Med. Assn., 1922, lxxx, 891–893.
22. Means, J. H., and Aub, J. C.: The basal metabolism in exophthalmic goiter. Arch, Int. Med., 1919, xxiv, 645–677.
23. Möbius, P. J.: (A note added to a review of a paper on the relation of polioencephalitis to Basedow's disease), Schmidt's Jahrb. d. Med., 1886, ccx, 237; Ueber Insuffizienz der Convergenz bei Morbus Basedowii. Centralbl. f. Nervenh., 1886, ix, 356–358; Ueber das Wesen der Basedow'schen Krankheit, Centralbl. f. Nervenh., 1887, x, 225; Die Basedow'sche Krankheit, Wien, Hölder, 1906.
24. Müller, F.: Beiträge zur Kenntniss der Basedow'schen Krankheit. Deutsch. Arch. f. klin. Med., Leipz., 1892–1893, li, 335–412.
25. Oppenheimer, B. S., and Rothschild, M. A.: Electrocardiographic changes associated with myocardial involvement. Jour. Am. Med. Assn., 1917, lxix, 429–431.
26. Peabody, F. W., Sturgis, C. C., Tompkins, E. M., and Wearn, J. T.: Epinephrin hypersensitiveness and its relationship to hyperthyroidism. Am. Jour. Med. Sc., 1921, clxi, 508–517.
27. Plummer, H. S.: The clinical and pathologic relationship of hyperplastic and non-hyperplastic goiter. Jour. Am. Med. Assn., 1913, lxi, 650–651.
28. Plummer, H. S.: Blood-pressure and thyrotoxicosis. Tr. Assn. Am. Phys., 1915, xxx, 450–457.
29. Plummer, H. S.: The function of the thyroid, normal and abnormal. Tr. Assn. Amer. Phys., 1916, xxxi, 128–133.
30. Plummer, H. S., and Boothby, W. M.: Specific dynamic action of thyroxin. Am. Jour. Physiol., 1921, lv, 295–296.
31. Plummer, H. S., and Boothby, W. M.: The cost of work in exophthalmic goiter. Am. Jour. Physiol., 1923, lxiii, 406–407.
32. Plummer, H. S.: Personal communications.
33. Wedd, A. M., and Stroud, W. D.: The spread of the excitation wave related to the standard electrocardiogram in the dog's heart. Heart, 1921, ix, 15–21.
34. Willius, F. A.: Arborization block. Arch. Int. Med., 1919, xxiii, 431–440.
35. Willius, F. A.: Myocardial disease with reference to the subendocardial myocardium. Med. Clin. N. Amer., 1919, iii. 653–659.
36. Willius, F. A.: Observations on negativity of the final ventricular T wave of the electrocardiogram. Am. Jour. Med. Sc., 1920, clx, 844–865.
37. Willius, F. A.: Electrocardiography and prognosis. I. Significant T wave negativity in isolated and combined derivations of the electrocardiogram. II. Aberration of the Q. R. S. complex in all derivations of the electrocardiogram. III. Significant T wave negativity and aberration of the Q. R. S. complex in all derivations of the electrocardiogram. Arch. Int. Med., 1922, xxx, 434–450.

REPORT OF A CASE OF MALIGNANT HYPERTENSION AND CERTAIN CLINICAL AND THERAPEUTIC FEATURES OF A SERIES OF CASES

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IN the large heterogeneous group of persons with high blood-pressure (essential hypertension, hyperpiesis, or cardiorenal hypertensive disease), a certain number possess an array of vascular signs and symptoms differing essentially in their severity from the remainder of the cases. Volhard and Fahr have recognized this difference, and on this basis have divided primary vascular disease into two groups: (1) benign hypertension, and (2) malignant hypertension. During the last sixteen months thirty-one cases of malignant hypertension have been studied in the Section on Cardiorenal-vascular Diseases, of the Medical Hospital Service of the Mayo Clinic. The relative incidence of malignant and benign hypertension is about 1 in 10.

The case reported herewith is illustrative of the classical features of this severe type of hypertensive disease, in the consideration of which points as follows should be noted: (1) evidence of probable primary vascular disease, (2) the high incidence of cardiorenal-vascular disease in the family history, (3) the resistance of this type of hypertension to treatment, (4) the temporary beneficial effects of prolonged hot baths on the systolic and diastolic blood-pressure, and (5) the low threshold of safety against intercurrent infection, in adequately functioning kidneys.

REPORT OF A CASE

Case 1 (A376907). Mrs. D. B. S., aged thirty-nine years, came to the Clinic November 8, 1921, complaining chiefly of indigestion, fatigue, and nocturia. She had had pneumonia, measles, and influenza between the ages of eight and twenty years, a definite attack of inflammatory rheumatism at

twenty-seven, and repeated attacks of tonsillitis, averaging one or two every winter. She had never been pregnant. About six years before she had been refused life insurance because of a slight increase of blood-pressure and mild albuminuria. No particular symptoms were noticed at this time, and the patient felt fairly well until one year before, when loss of weight and fatigue had become manifest. Dyspnea and weakness had begun to be definite about six months before examination, the dyspnea, 11 on a scale of 1 to 4, appearing on fast walking. The patient had noticed swelling of the legs at night; this disappeared by morning. Weakness had been progressive. The total loss of weight in one year had been 30 pounds. Her father had died of "kidney trouble" at seventy-seven. Her husband was living and well.

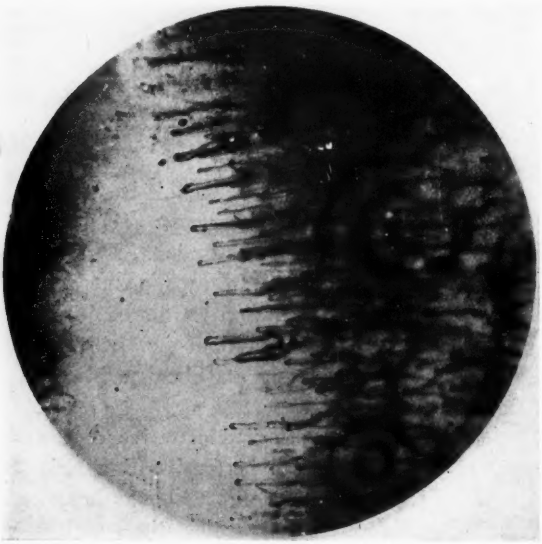


Fig. 47.—Photomicrograph of normal nail-fold capillaries (×50).

General Examination.—At the time of examination the patient complained of swelling of the ankles, numbness of the fingers on both hands, and occasional dizziness, particularly on change of posture. She had high color; the right pupil was slightly larger than the left; the tonsils were enlarged 2 with plugs, and appeared septic; considerable dental work had been done on the teeth; marked pulsation was observed in the right supraclavicular region, due to an elevated and tortuous subclavian artery; the left subclavian artery was palpable; aortic pulsation was visible in the suprasternal notch, where the artery was palpable, but not tender. The systolic blood-pressure was 246 and the diastolic 156. Both lobes of the thyroid were palpable. Findings in the lungs were negative. The heart measured 13 cm. to the left and 3 cm.

to the right. The apex was 12 cm. to the left in the sixth intercostal space. No thrills could be heard or felt. A systolic murmur could be heard in the mitral area, but was not transmitted to the axilla. P_2 and A_2 were accentuated 3. A systolic and presystolic murmur was heard in the pulmonary area, which was transmitted along the left border of the sternum, but no diastolic murmur was present in this area. The edge of the liver was palpable and soft. No pretibial or sacral edema was present. The uterus was definitely enlarged and hard, with a small palpable mass in the right fornix.

Fundi.—There was marked reduction, and irregularity of the caliber of the retinal arteries, engorgement of the veins, and marked arteriovenous

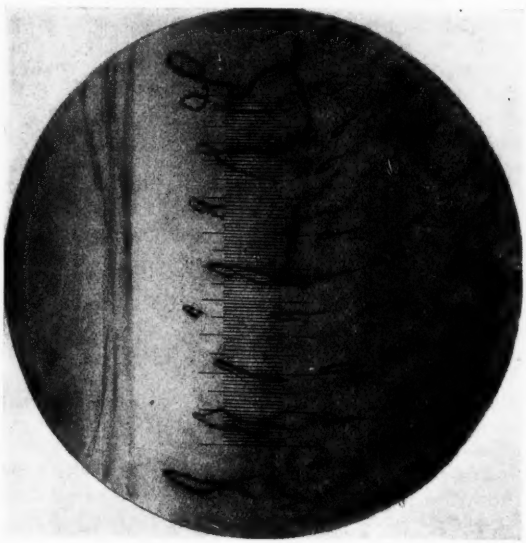


Fig. 48.—Drawing of nail-fold capillaries in a case of malignant hypertension. Note the fine or frequently invisible arterial limb. Nuclear or broken stream in all loops.

compression. The disk was edematous, the swelling measuring 3 to 4 diopters. The retina contained many exudates of the degenerative type. Diffuse, deep hemorrhages extended into the retina for a distance of several disk diameters, and there were areas of localized edema or cotton-wool exudate in the peripapillary region, more marked in the right eye, suggesting long-standing or recurrent retinitis.

Peripheral Vessels.—The temporal vessels were tortuous 2, and palpable 2; the radials were tortuous 1, full, easily rolled and compressible, and the brachials were palpable 2 and tortuous 2.

Nail-fold Capillaries (Figs. 47 and 48).—The nail-fold capillaries were

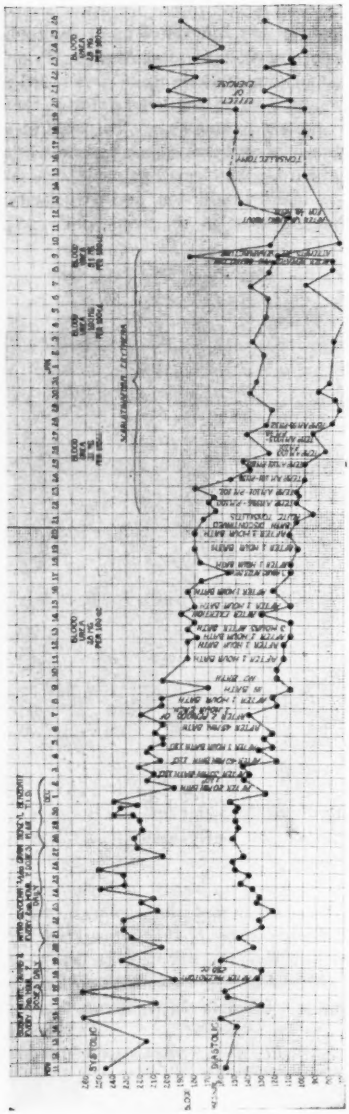


Fig. 49.—Blood-pressure levels for entire period of observation.

small and contracted, and difficult to visualize, the contraction being more marked on the arterial limb. The filling and emptying of certain capillaries was intermittent, slow, and not synchronous with the pulse or respiration. The arterial limb was extremely thread-like, and at times invisible. The capillaries occasionally had a hook-like appearance, instead of the usual hair-pin-like one. The capillary flow was visible and appeared nuclear. The flow often disappeared from the arterial entrance, with resulting disappearance of single or multiple capillaries. Occasionally a forceful or spurting type of flow was seen.

Renal Studies.—The specific gravity of the urine ranged from 1009 to 1023, with a constant trace of albumin and occasional hyaline and granular casts. The intravenous phenolsulphonephthalein excretion was 50 per cent in two hours. The uric acid in the blood was 3.5 mg., the creatinin 1.8 mg., and the urea 31 mg. for each 100 c.c. The hemoglobin was 75 per cent (Dare). The erythrocytes numbered 4,560,000 and the leukocytes 8800. The differential formula showed no change from normal. The basal metabolic rate November 21, 1921 was +33, and November 28, 1921 +12. Cultures of the urine revealed an occasional colony of Streptococcus hemolyticus. Roentgenograms of the chest revealed infiltration, more marked on the right side, probably an old healed lesion, and the dental roentgenogram showed one abscessed tooth. The electrocardiogram showed an inverted T wave in Leads I and II.

Subsequent Observations.—The patient was kept at absolute rest in bed for one week. At the end of that time the blood-pressure had not changed. Two hundred and fifty cubic centimeters of blood was withdrawn by phlebotomy. Sodium nitrite was administered, 2 gr. every two hours, four doses daily for a period of one week; the blood-pressure then varied from 210 systolic and 132 diastolic to 250 systolic and 138 diastolic. Benzyl benzoate, six times daily, in gram doses, was given for six days, but without demonstrable effect. At the end of the third week hot tub-bath treatment was instituted, commencing cautiously with temperature of 105 F. for ten minutes. The temperature and time period were gradually increased, the latter five minutes a day, the pulse, blood-pressure, and respiration being watched to avoid any untoward effects. At the end of ten days the patient was receiving two one-hour tub baths daily at a temperature of 110 F. The blood-pressure was reduced to from 185 to 155 systolic, and from 124 to 110 diastolic (Fig. 49). The patient was greatly relaxed, and symptomatically apparently much improved. The marked subclavicular pulsation had disappeared, and the aorta was barely palpable; the heart rate was slower and precordial pounding had disappeared. The capillaries of the skin were considerably widened, the rates of flow increased, and the general condition seemed greatly improved. The patient was extremely eager to continue the treatment, as she felt she was obtaining great benefit. While the hot-bath treatment was being carried on, 0.5 gr. of luminal was given twice daily. This treatment was continued until the end of the sixth week, when the blood-pressure ranged from 155 to 180 systolic, and from 100 to 105 diastolic. Three hours' immersion in baths was attained without untoward effects. During the last seven days the patient was allowed to be up and around, and to walk on an

average of thirty minutes a day. January 22, 1922 she had a temperature of 102, and the following day a severe tonsillitis. Marked generalized toxic erythema developed with considerable pruritis. The temperature continued high for nine days, during which time the blood-pressure dropped to 128 systolic and 70 diastolic. Although the blood-pressure was low, the patient felt weak, and there was evidence of marked asthenia. During the febrile period the renal functional studies revealed marked injury to the kidneys (Fig. 49), the albuminuria and cylindruria increasing greatly. No definite change of the nail-fold capillaries was noted during this period of low pressure and temperature other than slight dilatation of the loops and increased rate of flow.

Following the attack of tonsillitis the patient improved rapidly and the renal exacerbation subsided. Tonsillectomy was performed in face of known risks, without untoward effects, and the patient was kept under observation, and was allowed to be up and around for increasing periods each day. The blood-pressure varied from 160 systolic and 100 diastolic to 185 systolic and 130 diastolic. The patient felt well, and was allowed to return home, with strict instructions regarding long rest periods, limited activity, restriction of diet, and avoidance of infections. The continued use of the hot baths was urged. She did very well for a time after returning home, but died suddenly June 10, 1922; the exact cause was not determined.

Comment.—The attack of tonsillitis was unfortunate, and the injury to the kidney immediate. The low threshold of renal reserve was evident, in spite of the previous excellent functional capacity of these organs.

DISCUSSION

Cases of malignant hypertension may be divided into two groups: (1) those in which hypertension has been present for a variable period, and later in which is superimposed the clinical syndrome of the more severe type of high blood-pressure, and (2) those in which a severe hypertensive process runs a more acute fulminating course of usually two to four years' duration. It is impossible because of the lack of previous data on the blood-pressure to classify many cases in this manner. In many of our cases this grouping has been possible, as is illustrated by the patient herewith reported. Several of the cases in Group 2 were females with severe vascular injury and hypertension as a result of the toxemia of pregnancy.

The average age of the thirty-one patients was forty-four years; eleven were less than forty, three were less than thirty, and the youngest was twenty-six. The comparative youth of the patients is striking, and is in sharp contrast to the much

older average age of the patients with benign arteriosclerotic hypertension. Nineteen of the patients were males and twelve were females.

Etiologic Factors.—The cause of primary vascular hypertension is unknown, but probably the action of an unknown toxin on the vasomotor centers is responsible. Aside from the probable direct etiologic agent, there is a relatively high percentage of ancestral deaths from cardiovascular-renal disease. Eleven (36 per cent) of the thirty-one patients gave a clear-cut history of the death of one or both parents from either cerebral, cardiac, or renal disease. Undoubtedly, a more careful record of the deaths in the ancestry of patients of this type would reveal a material increase in this percentage. Osler believed that the quality of vascular tubing played an important part in the etiology of the condition. Recently Foster has touched on this phase of the subject.

Symptoms.—The most common general symptom in patients with severe hypertension is fatigue. This may be general malaise or inability to continue usual occupations with as much energy as formerly. Morning fatigue is often noted, and its association with a dull occipital headache is an important symptom which should direct attention to the cardiorenal-vascular system. Indefinite indigestion or gastric disturbances are often associated with a throbbing or dynamic abdominal aorta. However, many of the patients assert that they felt exceptionally well up to the time of the cardiovascular-renal break, which called attention to the gravity of the underlying condition.

The local symptoms are those referable to the heart, kidneys, or blood-vessels, these tissues showing the outstanding effects of the underlying degenerative disease. The organs most commonly involved in our series were the heart, the brain, and the kidneys, in order of their presenting symptoms. As a rule, the cerebral lesion is more common in older patients, but one patient aged thirty-one years had had epileptiform seizures, which were the earliest signs of the hypertensive disease. Slight cerebral seizures with transient paralysis, momentary mental lapses, and disturbance of memory were common. The ques-

tion of brain tumor often enters into the differential diagnosis. Other symptoms of vascular disease were tingling in the hands and feet, aural disturbances, dizziness, and roaring in the ears. Headaches were frequent and of two types: a dull aching sensation in the occipital area and a more diffuse pounding type localized in the frontal-temporal areas. In the cerebral group were certain mental disturbances, such as bewilderment, irritability, and lack of mental poise and concentration. Older patients had lost memory for recent events. In the chronic types of malignant hypertension the syndrome of cerebral arteriosclerosis was common, and on this were superimposed the more acute vascular accidents of malignant hypertension, either cerebral, cardiac, or renal.

The cardiac symptoms are usually marked and progressive. The intermittent types of cardiac breaks, as observed in certain other forms of heart disease, are not evident. A short history of dyspnea which rapidly progresses from that appearing with marked exertion to that appearing with the mildest types of exercise, is common. Often when such patients were hospitalized, marked orthopnea was present, even though the entire history of cardiac complaint was less than six months. Acute cardiac crises, probably of anginal nature, were observed, in which sudden seizures of substernal distress, marked orthopnea and evident mental distress, rapid respiration and sharp rises in blood-pressure occurred. The usual pain features of typical angina pectoris were not in evidence. These attacks would last from a few minutes to several hours. Usually the heart was markedly enlarged, with increased lengthening and widening of the aortic arch. This produces an elevation and subsequent elevation of the aorta and right subclavian artery. In these patients buckling of the right internal carotid artery was observed, occasionally simulating an aneurysm of the carotid. The aorta in the episternal notch was usually palpable, but not tender, and when treatment was temporarily successful, a marked subsidence of these vascular signs took place. The electrocardiogram revealed significant changes in 76 per cent of the patients. The most common change was an inversion of the

T wave in Lead I or in all theee leads. Slurring or notching of the QRS. complex was the next most common change. The T lead changes have a definite prognostic significance, as shown by Willius[5] and verified by the end-results in this series of cases.

The kidneys were not usually involved to the same degree as the cardiac and vascular tissues, as shown by the complete functional studies of these organs. Albumin with cylindruria was present in all of the thirty-two cases. In seven (21 per cent) there was marked renal insufficiency, as shown by the presence of an anemia, an intravenous phenolsulphonephthalein excretion below 25 per cent, and an excess of blood urea, more than 50 mg. for each 100 c.c. An impaired concentration function was found in this group, and in nine patients (28 per cent) a moderate involvement of the kidneys. In seventeen patients (53 per cent), there was only slight renal injury or none at all, and no functional defects could be demonstrated, but there was mild albuminuria with a few casts. This data favors the belief that hypertension is a primary disease of the arteries, and not necessarily the result of, or associated with, demonstrable renal disease, except in the cases in which the kidneys are the first tissues to break down. The kidneys suffer like many other organs. Moschcowitz has recently discussed the pathologic phases of this question, calling attention to the "minimal" pathologic changes found in the kidney.

The blood-vessels in every case revealed definite evidence of a degenerative lesion. The examination of the retinal vessels revealed hemorrhages and exudates, often with edema of the nerve head in all but two cases. The nerve head often simulated a choked disk, the swelling reaching 3 to 4 diopters. The peripheral vessels are usually lengthened and tortuous; they feel firm and very full, but compressible. Arteriosclerotic beading is not felt in younger patients. The temporals are full and throbbing. The nail-fold capillaries are small and fine and appear to be contracted. This is more evident in the arterial limb and is often so marked that the segment is invisible. Occasionally individual erythrocytes can be seen crowding through

a much too narrow vascular capillary channel. The frequent disappearance of the flow is noted, and suggests a spasmodic cutting off of the blood from the feeding arteriole. The blood-pressure values indicate the degree of vascular involvement, revealing excessive cardiac work and excessive peripheral resistance. Excessive values were obtained in the diastolic readings. In no case was the pressure less than 120. Disproportionate systolic-diastolic ratios were noted, as in one patient who had a systolic pressure of 180, and a diastolic of 135. As a rule, the excessive systolic values were in proportion to the high diastolic values. Diastolic readings as high as 170 mm. were obtained in one patient. The average systolic pressure was 240; the average diastolic, 148. These readings were the average of the initial readings for the first two days of hospitalization.

Treatment.—As the designation of this type of hypertension implies, resistance to treatment is the rule, and the results of the general measures employed in the treatment of this form of high blood-pressure are disappointing. In the cardiac cases, in spite of continued treatment, carefully supervised, the progressive breaking down of cardiac reserve continues. In cases of decompensation considerable transient improvement follows treatment with full doses of digitalis. Bleeding in fairly large amounts, 500 to 1000 c.c., is useful for its effect on certain disturbing symptoms, such as headache, dizziness, and cardiac crises, and moderate reductions of the blood-pressure for periods of six to twelve hours are observed. Following the administration of full doses of sodium *nitrite* given to the point of tolerance similar short remissions of symptoms are noted. The blood-pressure response to the *nitrites* and nitroglycerin was not marked in our case (Fig. 49). A low diet is usually prescribed, consisting of 1000 to 1500 calories, with low salt, and proteins restricted to 40 gm. If the patient is overweight, sharp reduction is sought, and the fluid intake is limited to 1500 c.c. Such patients are often in an extremely nervous condition when entering the hospitals, and sedatives in the form of morphin, bromids, or luminol are usually administered during the first three days.

A great measure of symptomatic relief is usually obtained by the carrying out of a rigid régime, such as that outlined. The marked throbbing of the heart and peripheral vessels with its disagreeable symptoms are alleviated. The dyspnea is diminished and the patients obtain a full measure of sleep and rest. This occurs without any decisive effects on the blood-pressure levels. Temporary periods of lowered blood-pressure may be obtained, but following slight exertion, or resumption of activity, the previous levels are reëstablished.

In several cases of this type, warm moist blanket-baths considerably reduced blood-pressure. Because of the short duration of the bath it was assumed that baths of longer duration and of fairly high temperature would augment this beneficial effect.

Treatment with hot immersion baths has been given with favorable subjective and objective effects. When the baths are instituted, a temperature of 105° F. for five minutes, two or three times daily, is used. The initial bath should be given with caution, the effects on the pulse-rate and blood-pressure being carefully observed. If well tolerated, the temperature is gradually increased, and the immersion period increased five minutes a day until a temperature of 110° F. for periods of three or four hours is obtained without irksomeness to the patient. In the case reported here a decided and fairly continuous lowering of the blood-pressure was obtained, as shown in Figure 49. When the patients leave the hospital arrangements are made, if possible, for the continuance of hydrotherapeutic treatment. The beneficial effects many patients obtain from treatment at warm springs are no doubt due largely to the relaxing effect of the hot-water baths.

No bad effects from prolonged hot-bath treatment were observed if certain precautions were taken. Marked cardiac decompensation is an absolute contraindication to this type of treatment. The question of increasing blood viscosity, with an increasing tendency to cerebral thrombosis, has been considered. Studies of the effect of immersion baths on blood viscosity are being made. Continued, prolonged immersion for many hours is

the goal to be sought, and when carefully started and controlled this treatment may result in considerable relief. There is no evidence that it markedly affects the final issue, but more vascular relaxation is undoubtedly obtained by this method than by any previous line of treatment.

Surgical procedures, such as removal of teeth or tonsils, incur considerable risk in this group of cases. Three of this series died elsewhere from uncontrollable hemorrhage following simple surgical procedures. No evidence is available which shows that removal of foci of infection retards the progressive downward course of this disease.

Prognosis.—The life expectancy in cases of this type of hypertension is short. Twenty-two of the thirty-two cases were traced within sixteen months. Twenty had died, three from hemorrhage following minor surgical procedures, four from cerebral accidents, four from cardiac insufficiency, and one from renal insufficiency. The cause of death was not stated in the other eight cases.

BIBLIOGRAPHY

1. Foster, N. B.: The relations of hypertension to cardiorenal diseases. Am. Jour. Med. Sc., 1922, clxiv, 808–819.
2. Moschcowitz, E.: Hypertension: its significance, relation to arteriosclerosis and nephritis and etiology. Am. Jour. Med. Sc., 1919, clviii, 668–684.
3. Osler, W., and McCrae, T.: The principles and practice of medicine. 9 ed. New York and London, D. Appleton & Co., 1921, 1168 pp.
4. Volhard, F.: Die doppelseitigen hamatogenen Nierenerkrankungen. Bright'sche Krankheit. Berlin, Springer, 1918, 576 pp.
5. Willius, F. A.: Electrocardiography and prognosis. I. Significant T wave negativity in isolated and combined derivations of the electrocardiogram. Arch. Int. Med., 1922, xxx, 434–450.

RADIUM AND ROENTGEN-RAY TREATMENT OF CHRONIC LYMPHATIC AND MYELOCYTIC LEUKEMIA

HARRY H. BOWING

CHRONIC leukemia is essentially a disease of the hemopoietic system, a mild or severe hyperplasia of the leukoblastic tissue with an increase in the number of luekocytes in the circulating blood. Two types predominate: chronic myelocytic leukemia in which the hyperplasia is limited grossly to the myeloid tissues with a great number of myelocytes circulating in the blood, and chronic lymphatic leukemia in which the hyperplasia is limited to the lymphoid tissues and with a great number of lymphocytes circulating in the blood. Acute leukemia is rare in the adult, but in children it is the predominant type.

In the majority of chronic cases the diagnosis is not difficult, but in a few the most vigilant observers fail to recognize the disease. A good history and careful physical examination with a detailed study of the blood is essential. Seldom, if ever, is it necessary to remove an enlarged gland for microscopic study and diagnosis. The cervical, supraclavicular, axillary, and inguinal glandular enlargements are typical of lymphatic leukemia, while an enlarged spleen is typical of myelocytic leukemia. The enlargements are bulky, soft and discrete, and vary in size in each anatomic space. They are never attached to the skin or underlying structures, never painful, and are free from the inflammatory processes usually noted in tuberculous adenitis. Abdominal glandular enlargements are seldom palpable. A roentgen ray of the chest in cases with respiratory complaints usually reveals mediastinal glandular enlargements, with or without concomitant complications.

The majority of patients are ambulatory, although weak

and unfit for their usual occupations; their appearance is pasty and anemic. An astonishing amount of glandular or splenic enlargement may be present without great discomfort, and with activities only moderately reduced.

For radiotherapeutic purposes the cases may be classified in two groups: (1) patients with small or scant superficial glandular or splenic enlargement, and slight or moderate change in the circulating blood-cells, whose general health is usually good, and (2) patients with extensive, bulky, superficial glandular or splenic enlargement, or both, with severe, excessive changes in the circulating blood-cells, whose general health is fair to poor, who are markedly weak, and have or do not have epistaxis, purpura, severe anemia, and so forth. There are many combinations of Groups 1 and 2, but for ordinary therapeutic purposes a more detailed classification is not necessary. It may be difficult to group a patient returning for treatment, but the condition the patient was in when first seen should always be kept in mind, since the duration of the disease is an all-important factor in treatment and prognosis.

TECHNIC OF TREATMENT

The technic of the treatment described herewith is safe and conservative, and has been employed in the treatment of about sixty cases in the Mayo Clinic. The universal silver tube applicator, walls 0.5 mm. thick, containing 50 mg. of radium element in the form of radium sulphate, or a brass tube, similar in design and equal in filtration, containing 50 millicuries of the emanation is used. No therapeutic preference is made, since, for ordinary purposes, the result will be the same. One or two tubes may be used in making a single applicator. The 50 mg. tube is most commonly employed. An additional filter of 2 mm. of lead is used. The lead disk measures about 2 by 3 cm. A similar one is placed above or over the silver tube for protection to the adjacent skin. Beneath this is placed a para rubber disk of the same size and thickness to absorb the secondary rays given off from the lead. In order to maintain the distance of 2.5 cm. from the skin a Balsa wood block is interposed. Its base is

about 3 by 4 by 2.5 cm. This wood is very light, which is an important factor in fixing and maintaining the position intended. Adhesive strips 1 cm. wide and 8 cm. long are sufficient to hold the parts of the applicator together. Adhesive strips 2 cm. wide and 20 to 25 cm. long are sufficient to fix the applicator to the body. The body area equals the size of the base of the block (3 by 4 cm.) (Figs. 50 and 51).

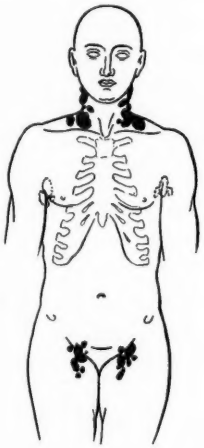


Fig. 50.—The superficial glandular masses occurring in the chronic lymphatic leukemia are represented by the solid black areas and the dotted areas in the right and left axilla.

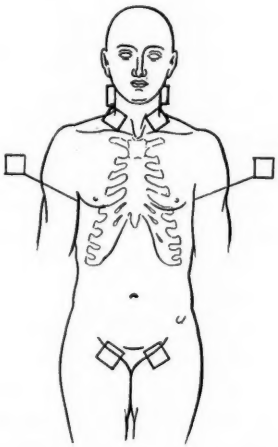


Fig. 51.—The small squares show the number and location of the radium applicator. One applicator is applied at a time and changed as recommended.

In myelocytic leukemia the splenic enlargement is the characteristic tumor; the number of areas (ports of entry) depend on the size of the spleen. The average number of areas is four, although six may be used. The maximal duration of the total application is twenty-four hours, or six and four hours respectively for each area. The minimal duration is twelve hours.

In lymphatic leukemia the superficial glandular enlargements are the most characteristic tumors. The maximal duration of application is twenty-four hours. Eight is the usual

number of areas treated: two each, in the right and left cervical region; one each, in the right and left axillary regions, and one each, in the right and left inguinal regions. Should the spleen be enlarged, two areas are mapped out over the enlargement, and only one area in each cervical space. The time exposure for each area is three hours. The applicator should be so placed that the bulk of the tumor is irradiated. The interval between treatments is usually seven days. On the fifth or sixth day following the last exposure the blood-cells are counted, the hemoglobin determined, and, if satisfactory, radium is reapplied on the seventh day. The number of treatments in one series varies from two to four, and the time interval between the series varies from six to eight weeks. The number of subsequent series depends on the response and its duration. The patient remains in bed during the exposure, and, when possible, is urged to be up and about between treatments.

This technic obviates all danger to the underlying and surrounding skin surface. The patient should be cautioned to keep the arm at a right angle to the body when the applicator is placed in the axilla; when the applicator is worn in the cervical area the head should be inclined toward the opposite shoulder, and when placed in the inguinal space the leg on that side should not be flexed on the body.

The formula described herewith has been used in only a few recent cases of myelocytic leukemia. The myelocytes in the circulating blood vary from 10 to 50 per cent. The main purpose of roentgen-ray exposures to the bones is to inhibit the presence of the circulating myelocytes. We are anticipating more prompt and enduring remissions. The ordinary standard roentgen-ray equipment and broad focus Coolidge tube, and the following factors are employed: 70 kv. (meter) 5 ma., distance 30 cm., filter 3 mm. aluminum, and time, five or six minutes. About twenty areas are exposed, treating two a day. The long bones and ribs are treated anteriorly and posteriorly, while the dorsal and lumbar vertebræ are treated only posteriorly (Fig. 52). The roentgenologic treatment is started early and continued daily until completed.

The plans of treatment must be individual, and most diligent coöperation between clinician and radiotherapist is paramount. There is no one factor to aid in deciding how much radium should be employed and the duration of the application. The amount

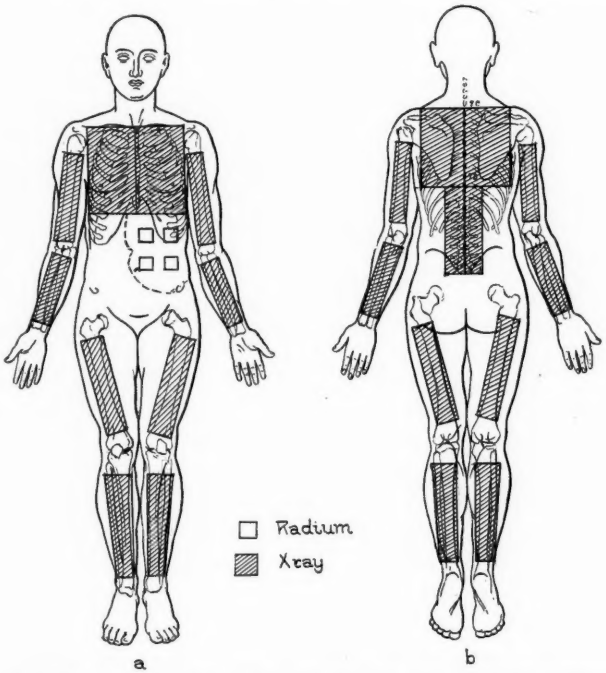


Fig. 52.—*a*, In chronic myelocytic leukemia the bones are exposed to *x*-rays. The rectangular spaces filled in with fine lines indicate the size, location, and number of ports of entry. *b*, The splenic enlargement is indicated by the broken line and the small squares show the location of the radium applicator. The number of areas vary from four to six, depending on the size of the spleen.

or extent of the glandular or splenic enlargement should not influence the formula. Reduction in size of distant glandular masses, as soon as the irradiated tumors are reduced, is commonly seen.

If the glands have suddenly enlarged within a few weeks,

with marked changes in the blood, usually with an abundance of premature cells in the circulating blood, not attended by much weakness, a 100-mg. applicator should be employed in an endeavor to reduce the activity of the process to a more chronic type. The blood-count and the general condition of the patient are probably the two most important single factors in deciding the amount of treatment. As soon as the leukocyte count diminishes, the patient begins to improve. In cases of hard, fibrous, splenic enlargements very little tumor reduction occurs. In most instances the tumors will reduce in two or three weeks following the radium application, and the reduction will persist for from two to three months. Observation from time to time and frequent examinations of the blood will determine the time for the next series.

The tendency to hemorrhage usually diminishes as the blood-count and general physical condition improve. In the young person the coagulating mechanism is delicately balanced, and too energetic treatment may precipitate a crisis. Epistaxis, petechial and purpuric eruptions, hematuria, and so forth, occur less often; the anemia usually improves. Should these conditions occur, blood transfusion should be given. Patients should receive symptomatic treatment. In the presence of anemia the recognized drugs to combat the process should be given. A combination of iron, arsenic and strychnin, or arsenic alone in the form of sodium cacodylate, hypodermically, are very effective remedies.

The improvement in some patients is remarkable, and if the treatment is judiciously applied, all will be benefited. Their appetite soon returns, the reduction of the tumors adds to their comfort; they sleep much better, gain in weight, and, when possible, should be kept up and about. It is better to apply 50 mg. for twelve hours and observe the patient carefully, than to apply 50 mg. for twenty-four hours and precipitate a crisis, especially in young adults, and patients in Group 2. As soon as the leukocytes in the circulating blood are reduced to from 20,000 to 30,000 all irradiation therapy should be discontinued.

The contraindications to treatment are usually determined

by examination of the blood; should the erythrocytes and hemoglobin dininish, treatment should be deferred, and a second examination of the blood made in from three to four days. As a rule, however, it is best to discontinue treatment as soon as this diminution occurs. A sudden drop in leukocytes should delay further applications until leukopenia can be ruled out. As the disease persists the remissions are less frequent and satisfactory; weakness, loss of appetite, chest complications, ascites and so forth occur, and treatment must be very cautiously given, if at all.

A local reaction in the skin, due to radium, will not occur with this technic. The systemic reaction, should one occur, is only mild. Nausea, occasional vomiting, headache, and slight increase in weakness may last for from twelve to twenty-four hours. The patient should be on a fasting diet twenty-four hours before and after treatment.

The effects of splenectomy as a procedure following the satisfactory reduction of the spleen with radium is now being carefully reviewed at the Clinic. In the splenectomized patient the liver may enlarge to great proportions. Radium cautiously applied to this tumor or roentgen-ray treatment of the bones, as mentioned above, will reduce the leukocytic count, and thus greatly add to the comfort of the patient.

BIBLIOGRAPHY

1. Giffin, H. Z.: Observations on the treatment of myelocytic leukemia by radium. Boston Med. and Surg. Jour., 1917, clxxvii, 686–691.
2. Giffin, H. Z.: Splenectomy following radium treatment for myelocytic leukemia. Med. Rec., 1918, xciv, 1020–1023.

HEMORRHAGIC PURPURA

HERBERT Z. GIFFIN
AND
JACKSON K. HOLLOWAY

HEMOPHILIA is not infrequently confused with hemorrhagic purpura. Yet usually the characteristics of these two conditions are distinctly different, especially so far as the laboratory findings are concerned. Hemophilia presents a prolonged coagulation time, a bleeding time which is usually normal, a normal platelet count, and a normal or prolonged prothrombin time. Severe hemorrhagic purpura presents a normal coagulation time, an irretractile clot, a prolonged bleeding time, a reduced number of platelets, and a prolonged prothrombin time. To reiterate, hemophilia shows a prolonged coagulation time; hemorrhagic purpura a normal coagulation time with soft clot. Hemophilia shows a normal bleeding time, hemorrhagic purpura a prolonged bleeding time. Hemophilia shows a normal number of platelets, hemorrhagic purpura a reduced number of platelets.

It must be remembered, however, that occasionally cases are seen in which a definite classification cannot be made. There may be a family history of bleeding, and yet the characteristics of hemophilic blood be absent. In other instances hereditary epistaxis may be severe, with no definite changes in the coagulation factors. In most cases, however, it is possible to distinguish between hemorrhagic purpura and hemophilia, and it is important to do so, especially from the standpoint of treatment. Surgical measures cannot be undertaken in cases of hemophilia, whereas in cases of hemorrhagic purpura the elimination of foci is not only possible, but necessary, when the patient is in proper condition for operation. Even major operations can be performed in the presence of hemorrhagic purpura; splenectomy

has been performed. The case reported here is one which demonstrates vividly the characteristics of severe hemorrhagic purpura, and shows the utter failure of medical measures.

Case 1 (A325237). A woman, aged twenty-three years, had had mild tonsillitis two years before, and diphtheria and scarlet fever in childhood. For the last two years she had been under thyroxin treatment for low-grade myxedema. She had been examined in the Mayo Clinic one year before, and was apparently well and healthy. Her menses commenced at the age of fourteen, had been somewhat irregular at times, usually lasting six days, and had always tended to be profuse.

The patient came to the Clinic January 9, 1922, complaining of weakness. For the last four months she had noticed numerous petechiæ on her arms and legs and body. For three months the menses had been almost continuous. At times there would be oozing only; again the flow would be so profuse that she would have to go to bed. For three weeks her condition had been very poor; she had been in bed most of the time, and was gradually getting weaker.

General physical examination revealed a very anemic and weak young woman, bleeding rather freely from the uterus and having numerous petechiæ on the body, but especially on the arms and legs. There was clotted blood in the left nostril, but no bleeding at this time. She was admitted to the hospital where the hemoglobin was estimated to be approximately 10 per cent, the erythrocytes numbered 1,100,000, and the leukocytes 12,200. She was given a transfusion immediately. Two days later the transfusion was repeated, but the uterine bleeding was not checked. Moreover, bleeding from both nostrils had commenced. This was controlled by packing the nostrils. Within five days two more transfusions had been given. Eleven days after admission there was no tendency for the bleeding to cease. Coagulen and coagulose were administered, but these too were without avail. It may be seen in Table 1 that the transfusions were, however, gradually improving the blood-picture, although the bleeding was not checked. Later the uterine bleeding ceased, but the bleeding from the nose continued. Fresh petechiæ were continually presenting themselves. Calcium chlorid was given intravenously in courses and repeated twice within two weeks. Nasal bleeding was fairly well controlled by packs which were removed every few days. The course of the hemorrhagic process was little altered, and two months after admission to the hospital, bleeding from the gums began and uterine bleeding recurred. Several small (50 to 100 c.c.) transfusions were given at short intervals. Radium (1800 mg. hours) applied over the spleen twice within two weeks, and intra-uterine radium (2200 mg. hours) were likewise ineffectual. Three blood-cultures had been negative. Most of the time during observation the patient had a remittent and intermittent temperature reaching as high as 103.5° F. April 24th, ten weeks after admission, the erythrocyte count reached its highest point, 3,170,000. In spite of transfusions, however, this count could not be maintained; by May 13th, four months after admission, the patient was exhausted, and bleeding continued in spite of all

efforts. She was growing definitely worse, and was allowed to return home. May 16th the erythrocyte count fell to 1,970,000. The patient gradually became weaker and died May 31st.

Table 1

Blood counts, transfusions, and coagulation tests

Date (1922)	2-10	2-25	3-16	3-25	3-30	4-12	4-18	4-21	4-24	5-1	5-9	5-13	5-16
Hemoglobin (per cent)	8-10?	23	28	32	40	45	42	40	43	43	42	28	17
Erythrocytes(millions)	1.11	2.56	2.02	3.04	3.09	3.55	3.02	3.04	3.17	3.09	2.74	2.05	1.97
Leukocytes	12200	15400	8700	7800	8500	8200	9000	8200	5600				
Lymphocytes	14.5					46.5		48.5	34.5				
Large mononuclears						1.0		2.5	1.5				
Transitionals	1.5					2.0		5.0	3.5				
Neutrophils	83.5					47.5		42.0	57.5				
Eosinophils	0.5					3.0		2.0					
Basophils								1.0	3.0				
Normoblasts	0.15												
Anisocytosis	Moderate							Moderate	Marked				
Poikilocytosis	Marked							Moderate	Marked				
Polychromatophilia	Severe							Marked	Marked				
Reticulated red cells	2.5							2.9	4.1	3.8		6.0	

Transfusions - patient in Group 2

Date (1922)	2-9	2-11	2-14	2-17	2-23	3-4	3-20	3-21	3-22	4-15	4-17	4-19	4-21	5-16
Amount, c.c.	500	350	400	500	400	500	50	60	50	50	50	50	100	400
C, citrate	C	C	C	C	C	C	D	D	D	D	D	D	C	C
D, direct														

Date (1922)	2-10	2-13	4-4	4-21	4-24	5-1	5-13
Coagulation time (Boggs)	7 minutes		7.5 minutes	10 minutes	6 minutes	8 minutes	9 minutes
Coagulation time (Lee)		4.5 minutes					
Bleeding time	1 hour 23 minutes		1 hour 10 minutes	2 hours 4 minutes	1 hour 22 minutes	1 hour 16 minutes	
		5.5 minutes					
Calcium time							
Prothrombin time (6 drops 0.5 $CaCl_2$)		10 minutes	23 minutes		2 hours		
Blood platelets		54000	64000	32000	26000	42000	22600

Purpura in itself is not essentially a disease. It is a symptom complex. This is true not only because the etiology has never

been established, but because purpura is so often observed in close alliance with various diseases. Petechiæ and purpura occur in cases of septic endocarditis, nephritis, leukemia, aplastic anemia, pernicious anemia, tuberculosis, and in a multitude of other diseases. There is a growing conviction that it is usually secondary to localized infection, and that in some way chemical toxins are formed as the result of bacterial action which affect the vascular tissues and the vascular elements in a very peculiar way. In many instances closer examination may disclose subacute infections, as of the teeth, tonsils, cervix, prostate, gall-bladder, and appendix. But far too little is known of focal infection in general and its relation to the blood and to purpura is an unexplored field. Many cases are frankly designated as toxic or infectious and the patients get well more or less promptly after the elimination of foci. This simple type of purpura, however, is capable of further development and may become transformed into a more severe form. In these more severe types the evidence of the initial infection may have disappeared, and a great deal of uncertainty exists as to whether or not hemorrhagic purpura should still be regarded as "idiopathic." In spite of the negligible findings at postmortem, the condition may be the result of a former infection.

The older classifications of purpura have been useful, but they are unsatisfactory. Henoch's purpura with abdominal pains, Schönlein's purpura, with joint manifestations, and Werlhof's purpura, with more generalized bleeding, are gradually becoming obsolete terms. Often one of these types merges into another, or a case may present symptoms common to all. Each type may be transitory, but is potentially chronic.

A hereditary factor has not yet been recognized, although purpura has been known to be more common in certain families. It might even be hypothecated that the infection which causes purpura can be transmitted from one member of a family to others, even of another generation. In the severe forms of purpura, papules or even vesicles and blebs may form. The mucous membranes, deep tissues, and the various organs may be involved. Rarely are extensive hematomas into connective

tissue or exudation into serous sacs observed. There is usually no tendency toward frank inflammation. The affected tissues, beyond showing interstitial extravasations and moderate hyperemia, usually appear normal. Amyloid and fatty changes have been described leading to hemorrhages by rhexis or diapedesis, but no definite cell destruction or endothelial change has been satisfactorily established. As to changes in the liver, spleen, marrow, and allied organs practically nothing has been demonstrated. In some instances the spleen is enlarged and its pulp is soft. Acute splenitis, with an increase of polymorphonuclear cells, has been described. There may also be a peculiar relationship between the volume of blood and the vascular apparatus, and between cardiac energy and capillary strength. Observers have speculated on the relationship of purpura to sepsis, to thrombolytic substances, to changes in the capillaries, to the influence of toxins and of hormones on the nerve supply of the capillaries, to changes in the blood itself, and the various angioneurotic phenomena.

In 1887 Denys noted that in the more severe forms of hemorrhagic purpura there was a marked reduction of blood-platelets, and that, within certain limits, hemorrhage depended on the number of these thrombocytes in the circulating blood. The physiology of coagulation and clot retraction depends, as we know, largely on an adequate number of blood-platelets, the border-line of safety being about 60,000. It is not known whether there is an increased destruction of platelets, a decreased production, or a localization of formed platelets within certain organs of the body. Certain it is that the most conspicuous abnormality within the blood itself is the markedly decreased number of blood-platelets in the peripheral blood. Since 1916 much work has been done to determine whether or not the spleen is responsible for the reduction in the number of platelets. It has been suggested that the spleen may produce a toxin which destroys the platelets, or a hormone which inhibits their formation. They have been observed in enormous numbers in spleens of affected persons. A marked difference in the number of platelets in the splenic vein as com-

pared with the number in the splenic artery has also been observed. In recent years, especially in Germany, this idea has been carried to a practical application. In several severe cases in which bleeding has threatened life splenectomy has been followed by splendid results. The hemorrhages cease almost immediately and there is a very rapid rise in the number of platelets to normal. In some cases a few days after splenectomy there has been a decrease in the number of platelets, then a more gradual rise to normal. Within a few months the number of platelets may even be well below the normal, although not so low as in the severe stage of the bleeding process; there is apparently no tendency to recurrence of bleeding or petechiæ. This later fall in the number of platelets would seem to indicate that the spleen is only one of a system of organs capable of either destroying platelets or producing substances capable of inhibiting their formation. It would seem, too, that the spleen is the chief of the system of organs involved, which leads us to suspect that the lymph glands, hemolymph glands, Kupfer cells in the liver, and possibly other portions of the reticulo-endothelial system are involved. When the spleen is removed there is probably a compensatory increase in activity of the other members of the group. It would appear, however, that their action never quite equals that of the spleen.

Assuming, then, that there is a toxic substance which destroys platelets and exerts a destructive influence on the capillary endothelial cells, and their nerve systems, and which is related essentially to the hemolymph system, of which the spleen is the major organ, it would seem that the toxic agent which acts on the vessels and blood itself is not the original organism, or its product, which initiated the pathologic process, but rather a resulting secondary product, perhaps an abortive substance designed originally to protect. The experimental production of antiplatelet serum whose action is specific, and by which we may produce experimentally what most closely resembles hemorrhagic purpura, leaves little doubt that the process is linked with protein intoxication. In mild cases of purpura the influence of this toxin may be merely sufficient to prevent

prompt regeneration of physiologically worn-out tissue cells. The delicate endothelial cells of the capillaries, instead of being replaced promptly and accurately, may suffer retardation. Petechiæ result mechanically. But here the toxin is insufficient to affect the platelets. There is no change in the coagulability of the blood. Hemorrhages do not result. The protective physiologic processes speedily make defense and repair damage. Hence the transitory nature of simple types of purpura. In the more severe forms the toxin may be more wide-spread in its effect. Reaction is more marked. Certain angioneurotic factors become involved. There is pain, swelling of joints, and erythema. In the severest forms, which may be classified as hemorrhagic purpura or thrombopenia, the toxic agent overwhelms not only the tissues of the vessels and the fixed body tissues, but influences the circulating cells also. Platelets, which, though short lived, are resistant, are destroyed and thrombopenia becomes an outstanding feature. Destructive changes allow blood to emerge from the small vessels, and because of the deficiency and abnormality of platelets, coagulation and retraction of the clot are incomplete. In most cases there are remissions during which the blood-picture returns toward normal. This points to the fact that there is probably no decreased production of platelets. The rapid rise in platelet counts within a short time after splenectomy, with abnormalities in size and shape, would rather favor the marked overproduction with rapid destruction of platelets.

In most instances the transitory character of purpura makes conservative treatment desirable. Many patients get well with little or no treatment, and many "cures" in all types of cases have been reported following the administration of various therapeutic agents, such as inorganic acids, iron, arsenic, calcium, coagulose, coagulen, thromboplastin, blood-serum, and transfusions. Foci of infection should be removed as soon as the patient's condition will warrant the procedure; and it is surprising that hemorrhage can be so easily controlled following minor surgical procedures. In the more severe types of purpura transfusions are usually necessary, and they are, as a rule, quite

effective in improving the anemia in spite of an increased amount of bleeding which may sometimes follow transfusion. Coagulose, coagulen, thromboplastin, and calcium chlorid intravenously may be given in courses, but are only occasionally effective. In the most severe types we can now affirm with a considerable degree of certainty that, when bleeding is persistent, and there is a reduction of the platelet count, a prolonged bleeding time and a non-retractile clot, splenectomy, in conjunction with transfusions before and afterward, is a life-saving procedure. Kaznelson has been a pioneer in this field. Cori and Ehrenberg have reported successful results. Minot reports a patient of this type to be in good general condition nearly two years after splenectomy. Brill reports two patients well six months after operation. Our own patient, operated on by C. H. Mayo in March, 1923, is in excellent health three months after operation, whereas one month preceding operation death would have been expected.

BIBLIOGRAPHY

1. Brill, P.: Article presented before the Association of American Physicians, Atlantic City, May, 1923.
2. Cori, G.: Zur Klinik und Therapie (Splenektomie) der essentiellen Thrombopenie. Ztschr. f. klin. Med., 1922, xciv, 356–369.
3. Ehrenberg, Charlotte: Ueber einen Fall von essentieller Thrombopenie und seine Behandlung durch Milzexstirpation. Monatschr. f. Geburtsh. u. Gynaek., 1920, li, 99–117.
4. Kaznelson, P.: Verschwinden der hämorrhagischen Diathese bei einem Falle von "essentieller Thrombopenie" (Frank) nach Milzexstirpation. Splenogene thrombolytische Purpura. Wien. klin. Wchnschr., 1916, xxix, 1451–1454.
5. Minot: Discussion before the Association of American Physicians, Atlantic City, May, 1923.
6. Steinbrinck, W.: Ein Beitrag zur Thrombocytenfrage. Ztschr. f. klin. Med., 1922, xciv, 447–458.

TRYPANOSOMIASIS: REPORT OF A CASE

THOMAS BYRD MAGATH

Case 1 (A397703). Mrs. L. F. W., aged forty years, presented herself at the Clinic July 11, 1922 for examination. The patient had lived in Africa when a child, and at intervals since 1911. She had had typhoid fever as a child. The present illness apparently dates from an attack of so-called malaria in 1919 while she was still in the Belgium Congo. The attack consisted of fever running as high as 104° F. for two or three weeks, with occasional intermissions of one day. No blood examination was made at the time. She returned to this country in January, 1920. On the way home she developed an eruption on her body and face, consisting of red rings 3.75 cm. in diameter, shaped like the letter C. The eruption did not cause itching; there was no sore throat, or general disturbance. On her arrival in this country she presented herself for examination in Boston, but no diagnosis was made. The eruption lasted from seven to eight weeks, toward the end of which time a general glandular enlargement appeared, involving the cervical, axillary, and inguinal glands. The glands are still palpable, although they are much smaller. Shortly after returning to this country she had two attacks of a malady which she thought to be malaria. The patient has never entirely recovered from this illness, and is unable to work. In February, 1921 she had a double otitis media which kept her in bed seven weeks. In October, 1921 the nasal septum was removed, and an examination was made for parasites in the blood, in another institution. During the winter the patient became weaker, and in March she became so weak that she was forced to go to bed. She lost her appetite and became somewhat drowsy. Rather suddenly she got better, but had a similar attack three or four weeks later. Since then she has had four or five attacks, all associated with drowsiness. Her last attack was three weeks before she came to the Clinic, and confined her to bed for eight or ten days. She was examined in Chicago, but no parasites were found in the blood or spinal fluid.

When examined at the Clinic the patient was thin and apprehensive. She weighed 122 pounds. There was a slight tremor of the hands, small black and blue spots were noted around the knees, and two circumscribed erythematous areas on the back. The pupils reacted to light and accommodation. The cervical, axillary, and inguinal glands were enlarged, firm, discrete, and movable, but not tender. The examination of the heart, lungs, and pelvis was negative; the spleen was palpable at the costal margin with a sharp, firm edge. When the patient was spoken to, she either answered slowly or not at all. She was drowsy, dropping into sleep rather readily, even while being talked to. The pulse-rate was 88, systolic blood-pressure 104,

and the diastolic 60. The temperature was 98.5. The neurologic examination revealed a slight increase in reflexes, definite tremor of the hands and arms, some hyperesthesia, and slight nystagmus. Examination of the urine revealed a slight albuminuria; other urinary findings were normal. The Wassermann reaction on the blood was negative. The hemoglobin was 60, erythrocytes 3,380,000, leukocytes 7600, lymphocytes 38 per cent, large mononuclears 5 per cent, transitionals 4 per cent, polymorphonuclears 47 per cent, eosinophils 5 per cent, and basophils 1 per cent. There was a slight basophilic stippling of the red blood-cells. Stained blood-smears disclosed the presence of *Trypanosoma gambiense.*

An axillary gland was removed and several trypanosomes were squeezed from it. The Wassermann reaction on the spinal fluid was negative, Nonne positive; there were 75 small lymphocytes, a few polymorphonuclears, and on centrifuging 10 c.c. of the spinal fluid two trypanosomes were found.

The patient was under observation for about one week; during this time her condition did not change, except that she became more nervous and restless. She was advised to go to the London School of Tropical Medicine, where she has received a course of treatment with Bayer 205. According to the latest reports she has greatly improved, the glands and spleen have returned to their normal size, her tremor has disappeared, and she is apparently well. No organisms can be demonstrated in the blood.

THE DISCOVERY OF TRYPANOSOMES

Sleeping sickness, the terminal stage of African trypanosomiasis, has been known for over a century. Trypanosomes were first found in cold-blooded vertebrates more than sixty years ago, and the first described species in a mammal was *Trypanosoma lewisi*, found in rats, by Lewis in 1879, in Calcutta. Evans, the next year, found *T. evansi* in horses in India, which causes "surra," a disease which for ages has been ascribed to the bite of certain flies. Bruce, fifteen years later, showed that "nagana," the "fly disease" of horses, bovines, and other domestic animals in Africa, was due to *T. brucei.* Since then trypanosomes have been found in fishes, reptiles, and birds.

Nepveu in 1890 found a protozoan in the blood of a man in Algeria, but because of his vague descriptions and crude illustrations it attracted no notice; however, later he emphatically affirmed that trypanosomes had to be reckoned with in tropical diseases in man.

Forde in 1901 found a flagellate parasite in a European suffering from an irregular non-malarial fever in the River

Gambia Colony. Dutton, a year later, identified it as a trypanosome, and called it *T. gambiense*, the name it now bears.

Castellani found trypanosomes in the spinal fluid and blood of patients in Uganda, and suggested that the parasite was the cause of sleeping sickness, which has been fully confirmed by Bruce, Nabarro, and others who have shown that the tsetse fly, *Glossina palpalis*, is the transmitter of the organism, a hypothesis previously advanced by Sambon and Brupt on analogic and epidemiologic grounds. Kleine in 1909 showed that the fly was not a mere mechanical carrier, but a true intermediate host. Later Stephens and Fantham established the fact that in Rhodesia another species of Trypanosoma existed, namely, *T. rhodesiense*, and Kinghorn and Yorke have proved it to be transmitted by *Glossina morsitans*.

MacFie has recently established the species *T. nigeriense*, transmitted by *Glossina tachinoides*, while Chagas has associated the Brazilian disease, derrengadera, with a trypanosome, *Schizotrypanum cruzi*, transmitted by *Conorhinus megistus*.

MORPHOLOGY, LIFE HISTORY, AND GEOGRAPHICAL DISTRIBUTION OF TRYPANOSOMA GAMBIENSE

This organism is a flagellated protozoan, which, when living in fresh blood, is an active wiggling organism, with a spindle-shaped body which is slightly compressed laterally and twisted spirally. It has a delicate undulating membrane, which fringes the convexities of the body, terminating at the anterior end in a flagellum.

When stained with Wright's stain the organism shows a central body known as the trophonucleus, and at the posterior pole a smaller, minute body, the kinetonucleus. The flagellum arises at the posterior end in a minute body, the blepharoplast, and passes anteriorly along the margin of the undulating membrane. There is a great variation in the measurements of individual organisms of this species, which range in length from 14 to 33 microns, and in breadth from 1.4 to 2 microns. Longitudinal division has been observed, and also small round forms. Artificial culture is very difficult and unsatisfactory, although

the disease can be transmitted to rats and other laboratory animals.

While it is probably true that if a tsetse fly feeds on an infected person, and within a few minutes bites another person, the latter will become infected, this would rarely take place, and no infection can be produced if the infected flies are kept for several hours before allowing them to bite another person. Sufficient time must elapse for the parasite to undergo development in the fly before the latter becomes capable of transmitting the disease. The parasite develops while passing through the fly's stomach to the posterior part of the hind gut. After ten to twelve days it passes to the proventriculus. Next the salivary glands are infected, probably about twenty days from the time the fly was infected. The flies are not infective until the glands are invaded.

The tsetse fly is a brownish insect about 8 to 13.5 mm. long, with a thick proboscis. The wings are quite large and marked like a marble fly. The fly is never found in the mountains, and is seldom seen above 3000 feet. It is also absent on plains and cultivated areas. Brush, trees, or forests are essential to its existence, and it is therefore sharply restricted to the banks of brooks or shores, or slow rivers and lacustrine islands. "Fly belts" are traced along narrow strips of forests along the edge of a stream, or a patch of "orchard brush." The eggs develop in the body of the fly until, when extruded, they are practically pupæ. The female deposits the larvæ singly, at intervals of two or three weeks, in loose, dry sand, humus or vegetable débris. The pupæ hatch in from four to nine weeks.

The flies feed on blood, exhibiting a fondness and voracity for man and mammals, both sexes taking part in the theft. *Glossina palpalis* and *morsitans* attack throughout the day.

T. gambiense has been found for the most part in the western part of Africa from Senegal in the north to Mossamedes and the upper reaches of the Lualaha in the south. It has been found in the Niger and Congo basins and in Uganda, and in the east has not extended much beyond the shores of Victoria Nyanza. At present it is bounded on the north by Kajo Kaji, at the

fourth degree N. parallel of latitude on the Nile, and inland by the southern and western portions of Bahr-el-Ghazel province, and on the south by the southern end of Lake Tanganyika.

SYMPTOMS OF TRYPANOSOMIASIS

The symptoms of trypanosomiasis may be briefly described as follows: Immediately following the bite of the insect a slight degree of local irritation and local swelling may be noticed. This subsides in a few days, is followed by fever which may last for a week or more, and, in Europeans at least, is accompanied by a peculiar type of erythema and serous infiltration. A form of hyperesthesia known as Kerandel's symptom is usual, though not constant. In time the fever subsides, to recur at irregular intervals of days or weeks, the fever sometimes running as high as 106.6° F., the evening temperature always being the highest. The fever may last for weeks, and is often quite irregular in its type and continuity. During this time headache is often complained of, and the heart's action is usually excited. Cervical glands and other glands in the body become tender and enlarged. Sometimes they are painless, rarely suppurating. This condition of irregular fever, general debility, adenitis, and slight anemia goes on for a matter of months or even years. Many cases may terminate at this stage, no further symptoms ever being present. However, in a large proportion of them local edema soon begins to develop, and various skin affections, such as papular eruptions and erythema, are noted. The type of erythema is rather characteristic, being annular, or in the form of a C. It is usually patchy and appears on the chest or back. During this stage there is more or less physical lethargy, fever of an irregular type being present. After some weeks or months the patient goes progressively downhill, and the condition known as sleeping sickness supervenes. Generally the first indications are emaciation, debility and languor, a slow shuffling gait, morose facial expression, and relaxation of features. The patient is slow to answer questions and shirks a day's work. Dull headache and fibrillar twitching of the muscles, especially of the tongue, develop, and the patient goes to bed. He does

nothing spontaneously, and seems to be content to sleep most of the time. Gradually the lethargy deepens, the body wastes away, bed-sores develop to a horrible extent, and the patient succumbs to convulsions, hyperpyrexia, pneumonia, dysentery, or some other intercurrent disease. There is considerable variation in this syndrome, but in general this is the typical progress of the course. Besides these rather typical symptoms, the final diagnosis of trypanosomiasis depends on the demonstration of the organism in the body of the patient. This is usually done by making blood slides, the blood being obtained from the lobe of the ear. In wet preparations the blood exhibits a remarkable clumping of red blood-cells, and if the organisms are present in fairly large numbers, they may be seen under the microscope as they disturb the erythrocytes, causing little currents in the films. In stained preparations the typical organism may be found even with the dry lens. In cases in which the organisms are few in number it is necessary to centrifuge citrated blood and examine the films made from the sediment in the ordinary way. Failing to discover the parasite in the blood, 10 or 20 c.c. may be withdrawn and inoculated into a guinea-pig, rat, or other laboratory animal. The organism may also be found in the cerebral spinal fluid, obtained by lumbar puncture, or by aspirating the large lymph-glands.

MORTALITY

While there may be spontaneous recoveries in the early stages of trypanosomiasis, once the sleeping stage has set in, recovery is rare, death being almost inevitable. When the disease occurs in epidemic form the population of whole areas may be wiped off, often numbering thousands of people. Some of the islands of South Africa, in Lake Nyanza, have been completely depopulated. The population of Uganda, originally about 300,000, was reduced in six years to 100,000 by sleeping sickness.

MORBID ANATOMY

The principal pathologic changes are microscopic, and are in the form of an extensive meningo-encephalitis. In some

cases there is congestion of the meninges, effusion of lymph, and turbidity of the spinal fluid. In all cases Mott has pointed out that there is an extensive small cell infiltration of the perivascular lymphatic tissue throughout the brain, cord, and meninges. Secondary degenerative changes in the nerves are also noted.

TREATMENT

The treatment of trypanosomiasis has, in recent years, assumed for the most part the form of administering certain types of arsenical compounds. At first atoxyl was given intramuscularly in 10 per cent solution, and was often administered in 7-grain doses every five days, until the symptoms subsided. More recently, however, antimony in the form of tartaric emetic has been advocated, to be used intramuscularly or intravenously, once a week. When using it intravenously, it is necessary to commence with 0.5 gr. dissolved in 10 c.c. of salt solution, and to increase by 0.5 gr. until a limit of 2 gr. for a single dose is reached. Great care must be used when administering it intravenously, since it is very toxic, and the patient must be under constant observation. Combinations of atoxyl and antimony have been used even more recently, but with none of these types of treatment have cures been effected once the patient has reached the sleeping-sickness stage. Various physicians have claimed good results when treating the earliest stages by this method. The drug which is attracting the most attention today in the treatment of trypanosomiasis is Bayer 205. Indeed, it has been stated that the country which controls its manufacture will control Africa. The treatment, as used by Dr. Philip Manson-Bahr, is to inject the drug in 1 gm. doses, intravenously, every week for ten weeks. The most recent indications are that this drug has a marked effect on the course of the disease, and that positive cures have been obtained by its use. The use of the drug is still in the experimental stage, however, and it will be some years before enough information can be accumulated to give it its proper place in the treatment of trypanosomiasis.

THE FACIES OF HEREDOSYPHILIS, WITH COMMENT ON ITS POSSIBLE EMBRYOGENESIS AND ITS CONFUSION WITH OXYCEPHALY AND CONGENITAL ECTODERMAL DEFECT

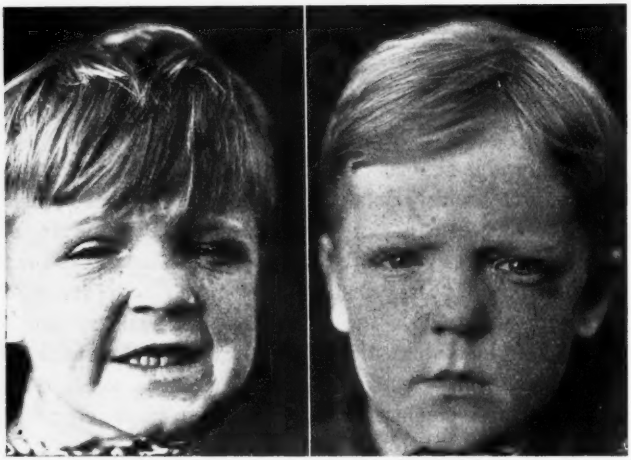
JOHN H. STOKES

THE analyzable stigmas of uterine syphilis as they affect the skull, the frontal and parietal bones, the nasal bridge, palatine arch, and teeth, when they are sufficiently marked to be singled out and identified as such, are reasonably familiar to the practising physician. There exists, however, a large group of borderline cases, in which the facial make-up, while no longer analyzable into individual stigmas, still creates an "impression." This impression, often spoken of as the "facies," seems much more familiar as a diagnostic aid to syphilographers, especially abroad, than it is to the medical profession at large. Textbook illustrations are few, and include usually only grossly obvious cases in which four or five obvious abnormalities appear. Yet the "impression" has high value in the detection of familial syphilis. Although it may not establish a diagnosis, it is an excellent arouser of suspicion and a stimulator of fuller investigation. As such it is invaluable and deserves to be better known.

In a sense, the impression or facies is, of course, a compound of stigmas; yet it is not entirely so. It is often impossible to separate the individual elements, yet the composite may be clear-cut and definite without the presence of a single typical herodosyphilitic stigma. The confirmation of the diagnosis in such cases is made by laboratory findings, and the study of the family.

The conversion of the impression produced by the facies of heredosyphilis into words is exceedingly difficult, and should be undertaken only with photographs and cases at hand. No

attempt should be made to use this "impression" for diagnostic purposes after an acquaintance based merely on verbal description. The most that should be expected of it is its use to stimulate interest and closer observation of case material by clinicians. The ultimate interpretations in debatable cases should be made



A *B*

Fig. 53.—*A*, The facies of heredosyphilis. The suggestion of apathy, lifelessness, fatigue, and "blurring" or "smudging" is not produced by focusing defects, for with a hand lens the lanugo hair between the brows and the delicate cleavage lines of the skin can be recognized in the original photograph. The boy had never had interstitial keratitis. The blood Wassermann reaction was positive. He had double dacryocystitis, which was practically quiescent when the photograph was taken. The "facies" is not lost by distortion of the lower face, nor is the forehead essential. In *B* the forehead is covered, there are no upper central incisors, and the "grin" showing the lower teeth does not conceal the impression.

by experts, and expertness can only be attained by seeing many cases under conditions which permit a full syphilologic check-up of suspected patients and their families.

The facies of heredosyphilis, like the "map" of a racial type, does not reside in any one feature. Repeated attempts to analyze it have led me to believe that the difference from the

normal resides in the part of the face above the upper lip, and even at times above the tip of the nose. A certain touch of fulness and excess breadth and height to the forehead is an element; yet rachitic and constitutional inferiority complexes may present it without giving the true impression. There is at times a suggestion of the Websterian "dome" and even of hydrocephaly, but this is not essential, and, in fact, may create false impressions if too much relied on.

Fig. 54.—A less pronounced, but nevertheless definite facies, estimated at 60 per cent. Note the look of fatigue and apathy, though the patient was well. She has a right upper central incisor, quite definitely of the syphilitic type, a negative blood Wassermann reaction, saber-shins, and interstitial keratitis. Her mother has a neurosyphilis of long standing.

The essence of the matter (Figs. 53, 54) lies in a certain inalertness, a sleepy, tired, fagged, clouded, dreamy or obscured appearance of the upper face, an appearance of veiledness, as if a smudge had lightly swept across the brows and eyes and the nasal bridge of a crayon portrait. It is possible to obscure the jaw and mouth with a card and still get an impression. Changes in expression or angle of inspection do not destroy it. Wile

has laid stress on the upward and outward flare of the nostrils, which results from the depression of the nasal bridge, and is undoubtedly important. To me this is less important than the apparent widening of the distance between the eyes produced by the recession of the nose.

Fig. 55.—The classical "map" of heredosyphilis, with all accessories, including bosses, corneal nebula, and Hutchinson incisors. Examination failed to reveal any evidence that this patient had ever had osteitis of the nasal septum to account for the flattened bridge.

Neither the cornea nor the teeth are essential to the impression, although clouding of the cornea from old interstitial keratitis (nebula) accentuates the impression, and the teeth may, of course, furnish the contributory touch or the final diagnosis (Fig. 55).

The facies of heredosyphilis is by no means unknown to art. An artist whose borders and headpieces have much vogue in

one of the popular magazines has a singular knack in his friezes representing the arts and industries, of reproducing quite unconsciously the veiled inalertness of the heredosyphilitic impression in the faces of the subjects in his industrial and bucolic scenes. Pressed a point further, with the brows more accentuated and the eyes deepened, with the blue iris and black pupil in sharp contrast, the facies becomes Celtic. I have seen the "map of Ireland" in a deaf girl cause a quandary among experts.

Like all diagnostic clues based on intuition, the facies of heredosyphilis must be cautiously interpreted and carefully controlled. It should never be used as the sole criterion for diagnosis, but must be supported by serologic evidence or actual stigmas, primary if possible, or a satisfactory combination of secondary evidence, including the study of the family. As a starting point for suspicion and a spur to fuller study of individual cases it is extremely useful. There is something that savors of the "black art" in the surprising confirmations that follow on the exercise of this intuitive power by the expert. It cannot, however, be said too often that it is impossible to learn the trick by merely reading from a book. It is only in the study of patients before and after confirmatory diagnosis, and in careful comparison with numerous examples of the confusion-producing pictures of rickets, adenoid facies, congenital anomalies, familial types and constitutional inferiorities that one can come to trust his instinct. Even with constant rechecking, especially after one or two brilliant finds, the observer may become hyperalert and see the facies of heredosyphilis in every bush. To prevent false clues it is best to check against another observer or two, habitually and if possible, independently, to prevent "talking up a case."

The differentiation of the heredosyphilitic facies from the other types just mentioned is not usually difficult. The box-head of rickets emphasizes one of the less important elements of the heredosyphilitic impression, the "dome." If there is nothing but a dome or a full forehead (Fig. 56), the impression cannot be trusted. The open mouth and vacant look of the adenoid type, with the signs of posterior nasal obstruction,

emphasize the lower rather than the upper face. Constitutional inferiorities, including idiocy, are caricatures on the human countenance which the facies is not. The large lustrous eye of the idiot, with its long lashes, the microcephaly, the tongue-sucking, drooling, and mental and facial blankness, have nothing in common with the facies of heredosyphilis. Mongols have the slit eye, the overlapped inner canthus, high cheek bones, and macroglossia which distinguish them.

Fig. 56.—Profile of the "dome." This abnormality alone does not constitute a "facies."

Familial resemblances at times materially modify an analysis of an impression, and, when possible, should always be taken into account. The resemblance to father and mother are, of course, the significant ones, and not those between the patient and his brothers or sisters. A verbal statement on the part of patient or parent cannot be wholly substituted for "confrontation," especially when it concerns distant and collateral relatives, or when the parent knows the purpose of the examination.

In the practice of the Section on Dermatology, in the Mayo Clinic, the facies forms one of the definitely recognized factors

in the diagnosis of uterine infections (familial syphilis). No member of the Section staff, however, passes an unchecked opinion on the facies. At least two or three opinions are collected. The presumption of heredosyphilis warranted by the facies is usually estimated in per cent (Fig. 54), to fit in with the other elements in the diagnosis. We have found the facies of special assistance in interpreting deafness in childhood, and in studying entire family groups, of which, unfortunately, it is impossible to illustrate any examples photographically.

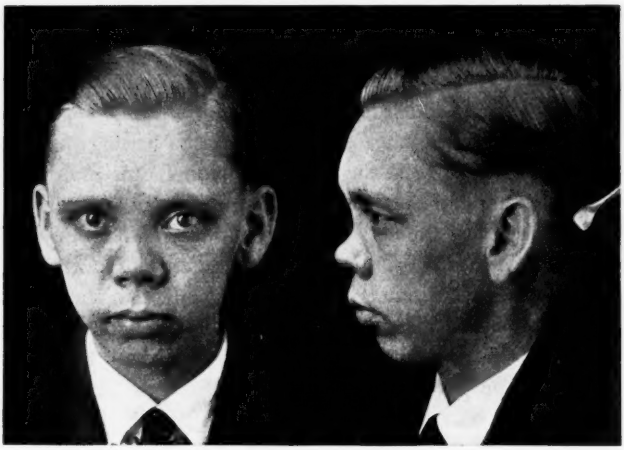


Fig. 57.—Deformity of the nose from collapse of the bridge, secondary to a destructive syphilitic osteitis of the nasal septum. This is not the heredosyphilitic "impression," although it may occur, as here, in heredosyphilis.

There are a number of reasons for believing that the facies described as heredosyphilitic should not be regarded as a syphilitic lesion produced by the actual presence of the *Spirochæta pallida* in the tissue of the affected part. The depression of the nasal bridge, and the "dome" forehead are developmental anomalies quite distinct from the falling of the bridge and distortion of the face, produced by gummatous osteitis of the nasal septum or osteitis of the frontal bones (Fig. 57). The broadened or depressed bridge may be present in patients who

show no signs of ever having had nasal syphilis (Fig. 55). The distinction, at times not closely enough drawn in text-books, is supported by the existence of anomalies such as oxycephaly and congenital ectodermal defect, which present clinical resemblances to the facies of heredosyphilis without convincing evidence of syphilitic etiology.

Embryogenetically, the parts of the face involved in the facies of heredosyphilis arise from the two anlagen of the frontal bones, and from the "incisor bud" from which develop the nose and the primitive intermaxillary bones. The fusion of the intermaxillary bones forms that part of the alveolar process from which arise the upper median and lateral incisor teeth. In a very suggestive study Nicolas and others have pointed out what they believe to be a distinct clinical syndrome of "syphilis of the incisor bud" and the osseous structures arising from it, among which they suggest the possibility of including as developmental anomalies the Hutchinsonian and other dental malformations affecting the upper median and lateral incisors. The influence of the *Spirochæta pallida* on the embryonal anlagen of this part of the face is conceivably a "toxic" effect on the osseous growth centers, or, as has been suggested, on the endocrine gland regulators of body growth. It probably antedates the actual formation of the parts involved, and consists essentially in the imparting of an abnormal twist or trend to the development of the embryonal tissues which results in the formation of a distorted part. Just how far back this twist may be exerted it is, of course, difficult to determine, but its ability to affect the anlagen of the second dentition teeth places it well within the earlier months of fetal life. This twist would seem to be beyond the reach of postnatal treatment, if one may judge from the development of Hutchinsonian teeth in children who have received treatment some months before the age (twelve months) at which the rudiments of these teeth are recognizable in the jaw.

During the last five years two especially instructive errors in the diagnosis of heredosyphilis from the facies have occurred in our clinical experience. In the first case the syndrome of

congenital ectodermal defect was confused with heredosyphilis. In the second, a diagnosis of heredosyphilis was made in a family group of a mother and two children who presented a mild grade of oxycephaly. In both cases the diagnosis was made largely from the facial make-up of the patients. The fact that the erroneous diagnosis in these cases was made by experienced clinicians, and the existence of conflicting views in the literature in regard to a syphilitic factor in these conditions, made it seem probable that this diagnostic error, if it is an error, deserves special consideration.

That the developmental twist which results in the facial and dental anomalies of the heredosyphilitic facies is not the exclusive product of an intoxication by the *Spirochæta pallida*, but may constitute a familial or inherent embryogenetic anomaly, is suggested by the occurrence of very similar changes in a familial group described as follows:

The group consists of a mother and two male children. The father had died by drowning two years before the children came to the Clinic. Fortunately, a group family photograph has been preserved which gives us an opportunity to trace familial facial resemblances. The mother brought the two children to the Clinic for hypospadias, with a diagnosis of heredosyphilis in the older boy, based apparently on a positive Wassermann reaction obtained by a physician who operated on the child for subdiaphragmatic abscess. No subsequent confirmatory Wassermann reactions were obtained so far as we were able to ascertain. The boy had been placed on treatment for syphilis by the physician who obtained the positive Wassermann reaction. When the boy entered the Clinic this presumption of syphilis was accepted perhaps too uncritically. In my own department the facies was regarded as sufficiently suggestive of heredosyphilis to justify a continuance of treatment for syphilis, although a provocative series of six blood Wassermann reactions was negative and the spinal fluid was normal. In accordance with our usual practice the mother and younger brother of the patient were at once subjected to searching examination for evidence of syphilis, and, in spite of a completely negative serologic

examination, including provocative blood and spinal fluid tests, the younger boy was also placed on treatment, again on the basis of facies and his brother's history.

I saw these patients for the first time toward the latter part of their course, and was at once struck by the unusual series of developmental anomalies which both children presented, and by certain deviations from type in their facies, which suggested the oxycephalic rather than the heredosyphilitic make-up. Further observation convinced me that the children, and the mother as well, represented mild grades of oxycephaly, and treatment for syphilis was accordingly suspended. The single point in the history supporting the diagnosis of syphilis was a history of miscarriage in the mother's first pregnancy, and the one positive Wassermann reaction said to have been obtained while the older boy was suffering from a subdiaphragmatic abscess. This I did not regard as convincing evidence, in view of the fact that false positive blood Wassermann reactions may occasionally be obtained in the course of febrile septic processes, to say nothing of the possibility of accidental false positives due to technical error.

The family history of the group is as follows: The paternal grandfather had died of tuberculosis. The father of the children had always been well up to the time of his death by drowning two years before. The mother of the children had always enjoyed good health. She had had one miscarriage at the fourth month, before the birth of the older boy. The older boy had had mumps and whooping-cough during the first year of life, and frequent tonsillitis and respiratory infections up to the age of six years. At the age of eight, he had sustained an operation for subdiaphragmatic abscess. At the present time his health is good and his mental and physical development good for his years, except for the abnormalities to be enumerated. The younger boy had likewise been of normal birth. He had had scarlatina two years before, and rubeola and pneumonia within the last year and a half. At the age of fifteen months he had had convulsions for one night only.

The presenting symptom for which relief was sought in both

children was hypospadias. The examinations of mother and children are paralleled below:

Mother.	Boy aged ten.	Boy aged seven.
Eyes far apart.	Eyes far apart.	Eyes far apart.
Nasal bridge slightly flattened.	Nasal bridge markedly flattened.	Nasal bridge moderately flattened.
	Supra-orbital ridges flattened.	Supra-orbital ridges about normal.
	High narrow skull.	High narrow skull.
No evidence of intracranial pressure.	*x*-Ray evidence of intracranial pressure.	*x*-Ray evidence of intracranial pressure.
	Prominent bony landmarks of skull.	Prominent bony landmarks of skull.
	High palatine arch.	High palatine arch.
	Large external jugular veins.	Large external jugular veins.
	Prognathism and adenoid facies.	
Tongue-tied.	Tongue-tied.	Tongue-tied.
Bifid uvula.	Bifid uvula.	Bifid uvula (right).
(Sister also has bifid uvula.)		
	Undescended testes (both).	Undescended testis (right).
	Double scrotum (2 sacs).	Single scrotum.
	Hypospadias (marked).	Hypospadias (marked).
	Strabismus.	Strabismus.
		Congenital heart lesion questionable. May be mitral insufficiency.
No evidence of syphilis.	No distinctive stigmas of heredosyphilis.	No distinctive stigmas of heredosyphilis.
Wassermann (provocative), spinal fluid reaction, and examination of eye-grounds and nervous and cardiovascular systems negative.	No other evidence of syphilis in Wassermann reaction, and so forth.	No other evidence of syphilis in Wassermann reaction, and so forth.

The familial resemblance of the boys to the mother was quite apparent, and was most striking in the group photograph of the

family taken when the children were smaller. In this picture (Fig. 58) the tendency toward an oxycephalic facies in the

Fig. 58.—From a family portrait, showing the familial, oxycephalic facies, and the resemblance to the mother's side.

Fig. 59.—A family group illustrating a mild grade of oxycephaly. The length of the face and the ears "on the neck" are better seen in profile, but the absence of supra-orbital ridges and wide separation of the eyes with the familial resemblances are apparent.

mother is much more apparent than in Figure 59. The lack of familial resemblance to the father is also apparent in Figure 58.

In discussing the question with the mother, she herself called attention to the fact that she and both her children were tongue-tied and had bifid uvulæ. On inquiry, she recalled that one of her sisters had a bifid uvula. This same sister has a child with a congenital hip. She remarked that everybody was inclined to comment on the striking resemblance between her boys and herself, although she had never noticed it.

Fig. 60.—The mottling of the shadow of the cranial bones, indicating pressure thinning. There is no osteitis. This is the younger boy in Figure 59.

There were no gross deformities of the skull in these cases. The fundus oculi in mother and children was entirely normal and there was no exophthalmus. No disturbance of vision was present, and the optic nerves entered the eyeballs at a normal angle. There were no signs of syndactylism, such as characterize the acrocephalic make-up.

The diagnosis of a mild grade of oxycephaly can be made in the children by the evidence of intracranial pressure in the roentgenograms of the skulls (Figs. 60, 61), and by the clinical

picture of high tower-like skull, disappearance of supra-orbital ridges, wide set eyes, prominent jugular veins, and so forth. The presumptive diagnosis of a still milder grade of the same developmental twist in the mother depends on the same wide separation of the eyes, most apparent in the family photograph (Fig. 58), on her obvious resemblance to her two sons, in whom the anomaly finally became outspoken enough for definite diagnosis, and on the presence in all three and in other members

Fig. 61.—Profile of skull showing a "mottling" in the same patient.

of the mother's family, of signs of an embryonal dysplasia, resulting in tongue-tying and bifid uvula.

Congenital Ectodermal Defect.—Our second case which tends to throw some light on the embryogenesis of the facies of heredosyphilis is one of congenital ectodermal defect (Fig. 62), reported by Goeckerman from this Section in 1920. The syndrome of congenital ectodermal defect includes an aplasia of hair and sweat glands, and certain anomalies in the development of the bones of the face and the teeth which strongly suggest those observed in heredosyphilis. While the reported cases of con-

genital ectodermal defect are few, a definite facies is recognizable, presenting collateral anomalies indicating a general embryonal dysplasia. The forehead and nasal bridge (Fig. 62) present changes so closely simulating those of a marked facies in heredosyphilis that it is difficult to escape such a diagnosis until the absence of hair and sweat glands is recognized. The dental anomalies are still more interesting. In certain of the reported cases there has been a total absence of normally formed teeth. In their place scattered conical "pegs" have formed, whose shape

Fig. 62.—The facies of congenital ectodermal defect. The patient had neither hair (wig) nor sweat glands and few teeth. Note the flattened nasal bridge. There was no osteitis or destruction of the septum.

quite suggests the extreme and final result of developmental anomalies detectable in milder forms in teeth modified by heredosyphilis.

SUMMARY

Observation of the cases here recorded suggests then that the facial make-up which is more or less distinctive of syphilis acquired *in utero* bears a definite resemblance to that observed in mild grades of oxycephaly and to the facies of congenital ectodermal defect. The dental aplasias and dysplasias of familial syphilis present clinical analogies to those observed in ectodermal defect. While the influence of syphilis in the two

latter conditions has been suspected, it is, however, far from proved, and the difficulties in the way of clinical demonstration of syphilitic etiology are well illustrated by the cases here presented. It would be presumptuous on the basis of purely clinical analogies to offer a theory of the embryonal mechanism involved. But it is at least suggested that the facies of heredosyphilis can scarcely be regarded as a syphilitic lesion in the sense that the *Spirochæta pallida* will be demonstrable in the tissues of the nasal bridge, or perhaps even in the anlagen of these structures. It seems much more probable that the influence of the spirochetal infection lies in the direction either of a direct disturbance of the growth centers, or of an influence on the as yet rather occult hypothetic endocrine mechanisms controlling prenatal growth and development. The cases of oxycephaly here discussed seem to indicate that the abnormal twist in development may begin at least a generation before the changes become pronounced enough for actual diagnosis. Witness the appearance of tongue-tying and bifid uvula, with a facies of a somewhat aberrant type in the mother of our group, and of actual oxycephaly accompanied by the same and other dysplasias in the two boys. One must, of course, allow place for the influence of third generation syphilis as a factor in the production of these dysplasias, but the evidence is at best very slender, and does not accord with observed stigmas and signs in what appear to be authentic cases of second generation syphilis. The consensus of opinion among students of the teratology of oxycephaly, acrocephaly, turricephaly and acrocephalosyndactylism seems to be against the acceptance of syphilis as a significant etiologic factor in these dysplasias, and Goeckerman found the same view to prevail in connection with congenital ectodermal defect.

The facies of heredosyphilis is then most conveniently regarded, in the absence of definite knowledge of the underlying developmental mechanism, as the result of a twist or embryonal dysplasia, the result of the syphilitic intoxication perhaps, rather than of the spirochetal invasion of the affected tissues as such. It should, therefore, be distinguished from the deformities induced by gummatous osteitis of the nasal and cranial bones. The

value of the facies in affording a clue to a heredosyphilitic factor in a variety of conditions in childhood and adult life should be better appreciated, but due precaution should be used in the interpretation of this element in a diagnosis. The possibility of confusion with the clinical picture of mild grades of oxycephaly and with the facies of congenital ectodermal defect should be borne in mind.

BIBLIOGRAPHY

1. Goeckerman, W. H.: Congenital ectodermal defect, with report of a case. Arch. Dermat. and Syph., 1920, i, 396–412.
2. Nicolas, J., Massia, G., and Dupasquier, D.: Le syndrome syphilitique du bourgeon incisif. Ann. de Dermat. et de Syph., 1922, iii, 6. s., 321–354.

OBSERVATIONS ON RETINAL ARTERIOSCLEROSIS

HENRY P. WAGENER

IN studying the retinal vessels in fundi in which there is no active, acute or chronic, inflammatory process, I have attempted to differentiate four types of arteriosclerosis: secondary, senile, primary, and consecutive.

SECONDARY ARTERIOSCLEROSIS

By secondary arteriosclerosis I mean the vascular changes remaining after the subsidence of various types of retinitis and neuroretinitis, and sometimes after choked disk. These are, in the main, reduction in caliber of both arteries and veins, more especially of the arteries; considerable irregularity in the lumina confined largely to the arteries; perivasculitis, often more marked in the veins, and at times arteriovenous compression, although this is more often seen in the presence of a coincident hypertension. The relative absence of exaggeration of the arterial reflex stripe is a distinguishing feature of this type of arteriosclerosis. The degree of these structural alterations is dependent on the severity and duration of the preceding inflammation. The irregular reduction in the lumen may go on to complete obstruction, and there may then be new vessel formation in the retina. Usually there are associated residues of the past process, such as pallor of the disk, general or localized atrophy of the retina, and scattered deposits of pigment, especially in the macular region; but all these may be absent, or may be present to a surprisingly small extent when the severity of the original inflammation is considered. It is this type of arteriosclerosis which is associated with the classical "albuminuric retinitis," both in its acute and chronic or end stages. In the acute stage the vessels are infiltrated with serum and

exudate, and often are difficult to distinguish in the surrounding retinal edema. In the end stages the changes described are seen.

According to Leber, the arteries and veins show, histologically, considerable thickening of the walls, partially through cellular infiltration and partially through hyperplasia of the tissue elements and proliferation of the interstitial connective tissue. Endarteritic proliferation of the intima plays a very essential part, and is the factor which leads to gradual narrowing and at last to closure of the lumen. Often in larger blood-vessels there is also considerable infiltration of round cells, particularly into the adventitia. This is seen in the retina as perivascular round-cell infiltration.

There is a type of secondary arteriosclerosis which is found in primary degenerations of the retina, such as retinitis pigmentosa. In this type the vessels, both arteries and veins, are uniformly markedly reduced in caliber throughout the fundus. In retinitis pigmentosa there is in addition pigment deposition along and in the walls of the smaller more peripheral vessels. The narrowing of the lumen in these cases, as seen pathologically, is not due to endarteritis, but to the deposition in the smaller vessel walls of an acellular substance probably secreted by, or otherwise derived from, the pigment cells, the larger vessels being functionally narrowed secondarily to the change in caliber of their terminal branches.

SENILE ARTERIOSCLEROSIS

Senile arteriosclerosis comprises those changes which occur in the retinal vessels merely in the course of growing old. It is comparable with the "decrescent arteriosclerosis" of Allbutt. Certain persons of seventy years or more have fundi that would be considered normal even in younger persons. There is, however, with increased age a tendency to decreased brilliancy of the retinal reflex, to gradual reduction in the apparent caliber of veins and arteries, and to the appearance of colloid deposits in the lamina vitrea in various locations, perhaps best grouped under the general, though rather incorrect, term, "guttate choroiditis." Determining the point at which this process

ceases to be a physiologic "growing older," and becomes a pathologic arteriosclerosis is often difficult, and a matter of judgment only. It is probable, however, that senile arteriosclerosis represents merely a more gradual application of the same causes which, acting rapidly and in large amount, produce true atheromatous arteriosclerosis, and that it should, therefore, be recognized as a clinical entity. Hence, when we see, in patients more than sixty years of age, arteries and veins reduced in size, the arteries more so, with slight exaggeration of the arterial reflex, but with regular lumina and no arteriovenous compression, we are inclined to interpret these changes as due to senile arteriosclerosis, especially if there are also present the senile pallor and loss of substance in the optic disk described by Fuchs, sclerosis of the choroidal vessels, and guttate choroiditis. Histologically, those vessels show thickening of the connective-tissue wall with increase of elastic tissue elements, while the endothelium remains unchanged. There is no actual narrowing of the lumen so that the apparent reduction in caliber seen ophthalmoscopically must be owing to the decreased transparency of the walls because of which less of the blood-stream is seen.

PRIMARY ARTERIOSCLEROSIS

The term "primary arteriosclerosis" is used to designate practically an endovasculitis, a disease primarily of the vessel wall, caused presumably by a toxin in the circulating blood, and comparable with the atheromatous sclerosis of the larger arteries in the general circulation and in the brain. This is essentially, both histologically and ophthalmoscopically, patchy in its distribution and may affect only one or many of the vessels. Histologically its basic pathology is that of localized subendothelial proliferation and, ophthalmoscopically, I think its most universal feature is a localized area of irregularity or reduction in lumen in an otherwise normal artery. In the early cases this may be all there is to be seen, although it is apt to be associated with irregular exaggeration of the arterial reflex due probably to localized thickenings of the vessel wall which will later produce reduction in the lumen. Another early sign, but

a more infrequent one, is corkscrew tortuosity of the terminal arterioles in the macular region. If the endarteritis is more generalized in a particular artery so that the wall is more or less thickened throughout a considerable portion, there will be more uniform reduction in caliber and more uniform exaggeration of the light reflex and, if the artery in its thickened portion crosses a vein, the vein will undergo what is spoken of as a right-angled compression, that is, the course of the vein will be temporarily altered so that it can take the shortest possible path under the artery and thus suffer the least possible obstruction to its channel. If the endarteritis affects a vessel in several closely situated patches only, there will be seen alternate contractions and dilatations producing the appearance of small aneurysms, or "beading," or broken exaggeration of the light reflex, this latter phenonemon possibly being caused by fatty degeneration in proliferated subendothelial nodules. If the process is more actively inflammatory, as it is, for instance, in syphilis, there will be more rapid and abundant proliferation of cells, and this may occur in the perivascular lymph sheath, as well as in the intima, so that perivasculitis is produced. This is comparatively rare, however, in the ordinary types of primary arteriosclerosis. The localized subendothelial proliferation first mentioned can go on to complete obstruction of the lumen, and thus the proliferation of new vessels and the other phenomena arising from thrombosis of the larger or smaller retinal branches can be produced. Various combinations of these individual changes form the composite syndromes which we call primary retinal arteriosclerosis. These are characterized by exaggeration of the retinal arterial reflex, often irregular, and producing beading; irregularities in the caliber of the retinal arteries; right-angled arteriovenous compression; tortuous terminal arterioles; areas of arterial obliteration; proliferation of new vessels, and perivasculitis. The dusky congestion of the disk (brick red) described by de Schweinitz is sometimes, but not always, characteristically seen. It must be remembered, however, that it is very seldom that the complete series is present in any particular case; and also that any single findings, unsupported, cannot be considered

as definitely diagnostic. The combination of any two or three, however, makes the diagnosis fairly safe. It is this type of arteriosclerosis with which the "arteriosclerotic retinitis" of Foster Moore is most frequently associated.

Of the histopathologic changes involved in this type of arteriosclerosis, Leber says: "In the more acute cases there is an endothelial proliferation by which the simple cell layer is converted into several layers of large voluminous cells on the internal limiting membrane. This proliferation is patchy in character as to its distribution, both around and along the lumen of the vessel. Some of the cells show fatty degeneration. After the proliferation is at an end, a normal endothelial lining and a new delicate elastica interna are formed within the proliferated lumen. In more chronic cases there is gradually formed, interior to the elastica interna, a layer of markedly flattened cells between which are numerous, delicate, elastic lamellæ. These elastic lamellæ gradually increase in thickness while the cells become less numerous. In the late course retrogressive metamorphoses can set in: hyaline degeneration, fatty degeneration, calcification, and amyloid degeneration."

CONSECUTIVE ARTERIOSCLEROSIS

By consecutive arteriosclerosis is meant arteriosclerosis that arises in the course of a general vascular hypertension, and presumably as a result of this hypertension. Here we are resting on less firm histopathologic grounds. As a rule, at least in text-books on the eye, the existence of this particular type of lesion is not recognized or observed as a separate entity, all retinal arteriosclerotic changes being grouped together. Apparently the retinal course and sequelæ of these last two types of arteriosclerosis differ even if the histologic findings are the same. It is in association with this consecutive type of arteriosclerosis that the scattered cotton-wool patches and hemorrhages constituting Benedict's "retinitis of hypertension plus nephritis" and the marked edema and flame-shaped hemorrhages of the retinitis of malignant hypertension are most common. Arteriosclerotic retinitis is seldom associated with this type of vessel

change, as the endarteritis rarely progresses to the stage of lumenal obliteration sufficiently to produce the characteristic areas of degeneration and hemorrhage. So almost universally true is this that the appearance of "arteriosclerotic type" exudates and hemorrhages in a fundus with only mild consecutive arteriosclerosis leads to the suspicion of the presence of diabetes, and usually hyperglycemia if not glycosuria is found. It is this type of retinitis which we regard as the typical diabetic retinitis. It corresponds exactly with Hirschberg's "central punctate diabetic retinitis."

Some of the changes seen in the retinal vessels in cases of hypertension are undoubtedly functional rather than organic. This is certainly true of the earliest findings: uniform exaggeration of the retinal arterial reflex confined often to the larger vessels only without reduction in caliber and often with slight dilatation, relative venous engorgement, and straight arteriovenous compression (that is to say, disappearance of the vein as it crosses under the artery and slight obstruction to the flow of blood without alteration of the course of the vein). These changes are characterized as "hypertension signs." They were recognized and described as such by Bardsley. In a later stage of the process there is uniform reduction in caliber of the retinal arteries with more marked exaggeration of the reflex stripe, but reduction in its width, while the relative venous engorgement still remains, and the arteriovenous compression becomes more marked. This change is considered by certain observers to indicate a functional contraction of the vessel walls to resist the increased tension. Others believe it to be due to an increase of fibrous tissue in the walls of the arteries, such as was described by Gull and Sutton under the term "arteriocapillary fibrosis." This seems to be the more rational explanation of the appearance, and at the Mayo Clinic we usually designate this ophthalmoscopic picture as "signs of hypertension with consecutive arterial fibrosis." In farther advanced cases, superimposed on the generalized reduction in caliber of the arteries, there are spots in which there is still further reduction, so that the lumina of one or more of the vessels show irregularities in various portions

of their course. These areas of constriction are considered by some to be produced by arterial spasm; but, to me, it seems more probable that they represent foci of subendothelial proliferation comparable to those seen in primary arteriosclerosis, and that there is present in these cases a true arteriosclerosis which has developed in the course of, if not actually caused by, hypertension. Consecutive arteriosclerosis, then, is characterized by exaggerated retinal arterial reflex, generalized reduction in caliber of the retinal arteries, irregularities of their lumina, relative venous engorgement, and straight arteriovenous compression. In it are never seen, at least without the introduction of an additional inflammatory factor, the beading, the proliferated new vessels, the corkscrew terminal arterioles, the perivasculitis, and seldom the areas of arterial obliteration of primary arteriosclerosis. Also, while the lumenal irregularity may be confined to one artery, the others all show some reduction and exaggeration of reflex at least, and are never completely normal as they may be in mild cases of primary arteriosclerosis. Occasionally cases are seen in which there is marked irregular reduction in the caliber of the arteries without exaggerated reflex and without much compression. The process involved must be endarteritic in nature and, while these cases are usually associated with hypertension, they may really belong to the primary type of arteriosclerosis.

DISCUSSION

Whether hypertension itself causes these arterial changes is a disputed point. Sir Clifford Allbutt thinks that there is an arteriosclerosis caused by hyperpiesia. However, this has never been definitely proved. In order to determine whether we could obtain any statistical proof of the etiologic rôle of hypertension in the production of retinal arteriosclerosis, I tabulated the findings with regard to a series of 200 consecutive patients examined in the Mayo Clinic during the spring of 1922, and diagnosed hypertension. A complete interpretation of the data obtained has not been attempted as yet, but a few of the apparent results are worthy of mention. In the study of the cases an attempt was made to make differential diagnoses along the lines

suggested in this discussion. The points of difference are not mathematically exact, and the diagnosis remains necessarily doubtful in some cases. The percentages given here are based on the presence of any type of retinal arteriosclerosis. The percentages of the individual types will be worked out later.

Of the 200 patients, 113 (56.5 per cent) had retinal arteriosclerosis, ninety-three (46.5 per cent) had general arteriosclerosis, and twenty-seven (13.5 per cent) cerebral arteriosclerosis. Of the group of 113, thirty-four (30 per cent) had no general arteriosclerosis; of the group of ninety-three, nineteen (20.4 per cent) had no retinal arteriosclerosis, and of the group of twenty-seven, seven (25.9 per cent) had no retinal arteriosclerosis. This seems merely to support the generally accepted view that arteriosclerosis is an irregularly distributed disease. One hundred forty-two of the 200 patients were more than fifty years old. Sixty-two and six-tenths per cent of them had retinal arteriosclerosis. Of the fifty-eight who were under fifty years, only 41.37 per cent had retinal arteriosclerosis. Again this supports a well-known fact, that arteriosclerosis is more common in old persons.

Sixty of the 200 patients came to the Clinic with symptoms directly referable to their hypertension and knowing that they had hypertension. Of these, 70.16 per cent had retinal arteriosclerosis. In the remaining 140 cases, the hypertension was discovered in the course of routine physical examination and its existence had not been suspected before, nor were there usually any subjective symptoms directly referable to hypertension. Only 50 per cent of these patients had retinal arteriosclerosis. These percentages would seem to indicate that hypertension, existing over a considerable period and of considerable severity, plays a part in the production of retinal arteriosclerosis. However, the idea is apparently not supported by the finding that, of the cases in which the hypertension had been known to exist for less than one year, 75 per cent showed arteriosclerosis, while increased duration of hypertension did not yield a corresponding increase in the frequency of arteriosclerosis. Thus of patients in whom hypertension had been present for from one to

two years, 70 per cent had arteriosclerosis; from two to three years, 50 per cent; from three to four years, 80 per cent; from four to five years, 78.5 per cent; and from five to twelve years, 60 per cent.

Of the patients who were over fifty years, twelve had systolic pressures below 165 mm.; of these 25 per cent had arteriosclerosis. Of the patients under fifty years, fourteen had systolic pressures below 165; of these, 21.4 per cent had retinal arteriosclerosis. Of the patients over fifty years, thirty-nine had diastolic pressures below 100; of these, 38.46 per cent had retinal arteriosclerosis. Of the patients under fifty years, twenty had diastolic pressures below 100; of these, 20 per cent had retinal arteriosclerosis. These data seem to show that it requires higher blood-pressure to produce arteriosclerosis in the young than in the old. This is probably explicable as an equation involving the height of the pressure, or its causative factors, and the time of action of the pressure or its causative factors.

In general, the findings do not seem to support the hypothesis that hypertension in itself mechanically causes arteriosclerosis. It seems more probable that there is a common cause for both, and that they are coincident symptoms, and not causative one of the other. It is of interest to note that of these 200 patients, twenty-four (12 per cent) had retinal hemorrhages without other signs of retinitis, nine (4.5 per cent) had nephritic retinitis of one type or another, seven (3.5 per cent), all of whom were over fifty years, had arteriosclerotic retinitis, and one (0.5 per cent), also over fifty years, had diabetic retinitis.

BIBLIOGRAPHY

1. Adams, P. H.: Arteriosclerosis and the eye. Brit. Jour. Ophth., 1920, iv, 297–318.
2. Allbutt, C.: Diseases of the arteries including angina pectoris. London, Macmillan, 1915, i, 280–371.
3. Bardsley, P. C.: The retinal signs of arteriosclerosis compared with those due simply to increased blood pressure. Brit. Jour. Ophth., 1917, i, 239–245.
4. Benedict, W. L.: Retinitis of cardiovascular and of renal diseases. Am. Jour. Ophth., 1921, iv, 495–499.
5. Benedict, W. L.: Retinitis of hypertension plus nephritis. Tr. Sec. Ophth. Am. Med. Assn., 1922, 33–43.

6. Fuchs, E.: Über senile Veränderungen des Sehnerven. Arch. f. Ophth., 1920, ciii, 304–330.
7. Gull, W. W., and Sutton, H. G.: Chronic Bright's disease with contracted kidney ("arteriocapillary fibrosis"). Med. Chir. Tr., 1872, lv, 273–326.
8. Leber, T.: Die Krankheiten der Netzhaut. Graeffe-Saemisch-Hess Handbuch der Gesamten Augenheilkunde, 1915, vii, pt. A1, 945 pp.
9. Moore, F.: The retinitis of arteriosclerosis and its relation to renal retinitis and to cerebral vascular disease. Quart. Jour. Med., 1916–1917, x, 29–78.
10. Parsons, J. H.: The pathology of the eye. London, Hodder & Stoughton, 1905, ii, 389–770.
11. de Schweinitz, G. E.: Intra-ocular angiosclerosis and its prognostic and diagnostic significance. Internat. Clin., 1907, i, 177–188.

GLOSSOPHARYNGEAL NEURALGIA*

JOHN B. DOYLE

GLOSSOPHARYNGEAL neuralgia is a clinical entity which, although relatively rare, is remediable; it is an exact analogue of trifacial neuralgia, and its distribution corresponds with that of the sensory portion of the ninth cranial nerve.

Early in March, 1922, my interest was directed to a case of severe paroxysmal pain in the throat, and between March 14th and June 1st I[1] examined four patients who complained of pain in the region of the tonsil, radiating to the corresponding ear, or to the ear and region around the angle of the mandible. In November two similar cases were examined. Recently, in the course of an exhaustive review of unusual cases observed in the Section on Neurology of the Mayo Clinic during the past three years, a seventh case was discovered.

REVIEW OF THE LITERATURE

In 1918 Vernet, in discussing the syndrome produced by involvement of the nerves passing through the jugular foramen, said that a destructive lesion of the ninth nerve causes paralysis of the superior constrictor of the pharynx which results in difficulty in swallowing solid food. Paralysis of the tenth nerve results in anesthesia of the soft palate and the posterior wall of the pharynx. Destruction of the accessory part of the eleventh nerve leads to paralysis of the soft palate and larynx, while destruction of the spinal portion produces paralysis of the sternocleidomastoid and trapezius muscles.

Trifacial neuralgia has long been accepted as a clinical entity.

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The characteristic paroxysmal pain, familiar to all neurologists and to most physicians, occurs in the area of distribution of one or more of the three divisions of the trigeminal nerve.

In 1907 and 1908 Hunt discussed in detail inflammations of a herpetic nature, involving the ear and adjacent regions. He attributed them to an involvement of the geniculate ganglion, similar to involvement of the gasserian ganglion and dorsal root ganglions in herpes zoster. The pain was different from that typical of tic douloureux.

In 1908 Orbison reported a case of herpes of the tympanic membrane and endeavored to prove the condition "due to zosteroid affection of the petrosal ganglion."

In 1910 Mills refuted Hunt's arguments concerning the nature of the afferent fibers of the facial nerve and attempted to show that the function of the nerve was chiefly gustatory, and that there was only a vestigial remnant of common sensation over a small portion of the anterior part of the tongue and a narrow strip in the auricle.

Lesions of the glossopharyngeal nerve, experimental or acquired, are extremely rare. In 1896 Meyer described the changes in the taste buds of foliate type, of the tongue of the guinea-pig, subsequent to section of the ninth nerve.

In 1919 Neve described a case of what he termed "herpes zoster of the glossopharyngeal nerve." The patient had palsy of the peripheral facial nerve on the left, impairment of the eighth nerve, a vesicular eruption over the left half of the soft palate, and pain posterior and inferior to the left ear and down the left side of the neck.

Oppenheim described a case of paralysis of the ninth nerve in a woman. Objectively she had thermasthesia, paresis of the soft palate and pharyngeal muscles, and loss of taste in the soft palate, pharynx, and posterior part of the tongue. Tactile sense was preserved intact.

In 1910 Wiesenburg described a case of cerebellopontile tumor diagnosed for six years as tic douloureux. Frazier cut the sensory root of the fifth nerve and excised most of the gasserian relatively early, to relieve what appeared to be trifacial

neuralgia. Following this operation the patient complained of pain in the right side of the throat radiating into the ear and neck and occasionally to the shoulder; later he had severe paroxysmal pain at the root of the tongue and in the right side of the pharynx, initiated by the contact of food or other foreign material with the mucous membrane of the pharynx. He also complained of pain in the lower right side of the face. It should be emphasized that the character of the pain differed after the ganglion operation, in that the pain before operation was in the whole face as well as in the throat. Repeated pharyngeal and laryngeal examination revealed excessive tenderness on the right side, but no weakness of any of the muscles of that region. At necropsy a tumor was discovered in the right cerebellopontine angle, lying directly on the sensory and motor roots of the fifth nerve. The ninth and tenth nerves, which were very prominent, stretched over the lower portion of the tumor. On account of the close relationship of the peripheral fibers of the fifth and ninth nerves, Weisenburg interpreted the pain which persisted in the area of distribution of the fifth nerve after resection of the major portion of the gasserian ganglion as a result of irritation of the ninth nerve. The pharyngeal pain was also attributed to irritation of the ninth nerve.

Under the caption "Neuralgien des Glossopharyngeus," Siebert has described three cases of paroxysmal pain in the pharynx and the root of the tongue following angina.

In 1920 Sicard and Robineau described three cases of what they termed "algie velo-pharyngée essentielle." The first two cases were seen in the French army in 1916 and 1917, respectively. In one case the pain was on the right side; in the other, on the left. In neither case could a cause be established. There was no antecedent history of syphilis, and the condition did not respond to treatment for syphilis, to sedatives, or physical agents. In both cases the pain had persisted over a period of several years; it was not continuous, but recurred frequently day and night in extremely acute paroxysms on the least motion in mastication, deglutition, or speech. Occasionally the paroyxsms occurred spontaneously. The patients developed suicidal ten-

dencies on account of the apparent incurability of the condition.

The treatment advised consisted in section of the glossopharyngeal nerve and the pharyngeal branches of the vagus, with ablation of the superior cervical sympathetic ganglion. These two patients were operated on by surgeons unfamiliar with surgical procedures in the neck. In one, the ninth nerve was cut, the sympathetic ganglion was removed, and the trunk of the vagus severed; in the other, the ninth and twelfth nerves and the pharyngeal branches of the tenth nerve were cut, and the sympathetic ganglion was removed. Both of the patients convalesced rapidly. The first patient developed unilateral palsy of the vocal cord; the second, hemiatrophy of the tongue.

Sicard's third case was that of a woman, aged fifty years, in whom Robineau successfully cut the ninth nerve and the pharyngeal branches of the tenth, and ablated the superior cervical sympathetic ganglion. During operation the trunk of the vagus was pulled, resulting in paresis of the homolateral vocal cord; this condition, however, was steadily improving. As in the first two instances, all pain disappeared immediately following operation. The first patient has been completely relieved for four years and the second for three.

Harris has recently described two cases of a rare form of chronic paroxysmal neuralgia, which he termed "glossopharyngeal neuralgia." The pain, according to him, characteristically starts in the throat in the region of the tonsil and anterior pillar and radiates to the ear and upper part of the neck. The first case was that of a man, aged forty years, whom he had first seen ten years before, when he successfully injected the third division on the affected side without influencing the pain. The second patient was a woman, aged eighty-seven years, who had suffered from the condition for ten years. Harris was convinced of the involvement of the ninth nerve in these cases; he had seen a man with similar pains and intense hyperesthesia of the side of the neck, following a recurrence of epithelioma of the tonsil seven years after extirpation of a malignant vocal cord.

ABSTRACT OF CASE REPORTS

Case 1 (A386270). W. H. L., a farmer, aged sixty-three years, came to the Clinic, March 14, 1922, complaining of pain in the throat and right ear. Five years before, after taking a drink of cold water, he had had a sharp paroxysmal pain in the region of the right ear, associated with excessive tenderness of the right auricle. Similar seizures occurred sporadically until 1918, when his tonsils were removed. He was completely relieved for about three years; then, for six months, he had mild paroxysms. Following the extraction of several infected teeth in the fall of 1921 he was relieved until the last week in February, 1922, when the pain recurred while he was drinking water. He had great difficulty in obtaining sufficient nourishment, owing to the pain induced by drinking and masticating. The pain was paroxysmal, sharp and agonizing, arising in the right faucial region and radiating laterally to the area anterior and posterior to the right ear; it lasted from thirty to ninety seconds and was definitely increased in frequency by talking and chewing. At the onset the attacks had come on during the night; in the two weeks preceding his examination his distress had been chiefly diurnal.

The physical examination was negative except for slight arteriosclerosis and moderate enlargement of the prostate. Both fundi were negative except for slight choroidal sclerosis. The Wassermann reaction was negative, as were the urinalysis, blood counts, and stereoscopic roentgenograms of the head. On examination of the larynx and nasopharynx a trigger area was discovered deep in the hypopharyngeal region. The only neurologic findings were a slight to moderate diminution in perception of vibration and slight incoördination of both lower extremities. The neurologic diagnosis was trifacial neuralgia involving the auriculotemporal branch of the right mandibular division.

March 23, 1922 the sensory root of the right gasserian ganglion was cut, and the motor root preserved. The patient was greatly relieved. April 14th he returned to the Clinic. The pain had been recurring for the last forty-eight hours. During examination the paroxysms were almost continuous. Morphin, hypodermically, gave but little relief. April 25th the glossopharyngeal nerve was avulsed and the pharyngeal branch of the vagus cut. For the last ten months the patient has not had a recurrence of the pain.

Case 2 (A387492). F. W. McC., a man aged fifty-two years, came to the Clinic March 28, 1922, complaining of a dull throbbing pain of two weeks' duration, in the region anterior to the right external auditory meatus, associated with paroxysms of sharp, stinging pain in the right side of the throat and right ear.

Injection of the mandibular division of the fifth nerve and the auriculotemporal nerve did not influence the pain.

Case 3 (A118335). E. M., a woman, aged fifty-seven years, came to the Clinic May 2, 1922, complaining of pain in the throat which radiated to the angle of the right mandible. She had been perfectly well until the summer of 1921, when she developed occasional, mild, paroxysmal pains lasting a second or two, originating in the right side of the throat and radiating to the

angle of the right mandible. After six weeks they disappeared, only to return April 10, 1922, following a drink of cold water. The paroxysms were of moderate severity and occasionally occurred in series. Unfortunately, this patient left the Clinic before her examination was completed.

Case 4 (A388607). J. H., a man, aged sixty-one years, came to the Clinic, April 10, 1922, complaining of pain in the region of the left external auditory meatus. He had had attacks of paroxysmal, sharp, stabbing pain lasting a few seconds in five periods of ten or twelve days' duration during the past nine years. The pain was in the region inferior and posterior to the left, external, auditory meatus, and was associated with a sense of irritation in the left, lateral, pharyngeal region, and a hacking cough.

Operation was performed May 30, 1922. The pharyngeal branch of the tenth nerve was accidently cut, but the glossopharyngeal nerve was not injured. The pain continued for four or five days, after which it subsided. For three weeks during August, 1923 the patient had a recurrence of the typical paroxysmal pain.

Case 5 (A409317). J. O. A., a man, aged thirty-eight years, came to the Clinic November 1, 1922, complaining of paroxysmal pain originating in the left tonsil and radiating to the region of the angle of the left mandible and the left ear. The pain, which was "cramp-like, cutting and tearing," had recurred about twice annually for seventeen years in periods varying in duration from one day to nine months.

The patient was seen during a remission and was advised to return for operation should the pain return.

Case 6 (A409512). A. A., a man, aged fifty-two years, came to the Clinic November 3, 1922, complaining of sharp, deep-seated, paroxysmal pain radiating from the right tonsillar area to the right ear, and occurring in four periods varying in length from one day to three months, during the past four years. Complete symptomatic relief followed avulsion of the right glossopharyngeal nerve.

Case 7 (A368977). J. P. S., a man, aged fifty-six years, came to the Clinic August 19, 1921, complaining of paroxysmal pain in the pharynx radiating to the angle of the left mandible and to the left ear, which had recurred in periods of three weeks to one year in the preceding ten years. In the course of a series of paroxysms the patient occasionally suffered with hiccup. The pain was lancinating in character, and excruciatingly severe. This case was described by the examining neurologist as a "syndrome as definite as tic douloureux." A definite clinical diagnosis was not made.

DISCUSSION

The distribution of pain in the first two cases was considered atypical, but the paroxysms were exactly like those of trifacial neuralgia. Following the recurrence of pain after section of the sensory root of the gasserian ganglion in the first patient, and after unsuccessful alcohol injections in the second patient, it

became apparent that the condition was similar to trifacial neuralgia, but that some nerve other than the trigeminal was involved. Harris' discussion of glossopharyngeal neuralgia convinced me that the patients were suffering from that disturbance.

Pain due to irritation of a root ganglion is usually paroxysmal, sharp, and cutting. The "shooting pains" of tabes, the pain of herpes ophthalmicus, of herpes oticus, and frequently of herpes zoster, as well as of an occasional tumor of the gasserian ganglion (Case A404414) are similar in their various locations to the pain of trifacial, glossopharyngeal, and paroxysmal occipital neuralgia. Paroxysmal pain occurring in the distribution of a given nerve may be considered as having its site of origin in the corresponding ganglion. Experience with trifacial neuralgia has taught us that permanent relief from such pain can be obtained only by section of the posterior root of the offending ganglion. Avulsion, the operation proposed and performed, cannot, therefore, be considered ideal. Sooner or later the patients will probably have recurrences of pain. In the interim, however, let it be hoped that surgeons will have perfected a technic as good and as safe as that of the modern operation for section of the posterior root of the gasserian ganglion, at the same time preserving the motor branch of the trigeminal.

CONCLUSIONS

1. Glossopharyngeal neuralgia is a definite clinical entity, differing from trifacial neuralgia only in the area of distribution of pain.

2. Paroxysmal pain which is definitely limited to the area of distribution of a sensory nerve may be considered as evidence of irritation of the corresponding ganglion.

BIBLIOGRAPHY

1. Doyle, J. B.: A study of four cases of glosso-pharyngeal neuralgia. Arch. Neurol. and Psychiat., 1923, ix, 34–47.
2. Harris, W.: Persistent pain in lesions of the peripheral and central nervous system. Brain, 1921, xliv, 557–572.

3. Hunt, J. R.: On herpetic inflammations of the geniculate ganglion. A new syndrome and its complications. Jour. Nerv. and Ment. Dis., 1907, xxxiv, 73–97.
4. Hunt, J. R.: A further contribution to the herpetic inflammations of the geniculate ganglion. Am. Jour. Med. Sc., 1908, cxxxvi, 226–241.
5. Meyer, S.: Durchschneidungsversuche am Nervus Glosso-pharyngeus. Arch. f. mikr. Anat., 1896, xlviii, 143–145.
6. Mills, C. K.: The sensory functions attributed to the seventh nerve. Jour. Nerv. and Ment. Dis., 1910, xxxvii, 273–285; 355–380.
7. Neve, C. T.: Herpes zoster of the glossopharyngeal nerve. Brit. Med. Jour., 1919, ii, 630.
8. Oppenheim, H.: Quoted by Weisenburg, T. H.
9. Orbison, T. J.: Herpes of the membrana tympani: due to zosteroid affection of the petrosal ganglion. Jour. Nerv. and Ment. Dis., 1908, xxxv, 500–506.
10. Sicard, R., and Robineau: Algie vélo-pharyngée essentielle, traitement chirurgical. Rev. neurol., 1920, xxvii, 256.
11. Siebert, H.: Ueber Erkrankungen peripherischer Nerven. Monatschr. f. Psychiat. u. Neurol., 1921, xlix, 364–370.
12. Vernet, M.: Syndrome du trou déchiré postérieur (paralysie des nerfs glosso-pharyngien-pneumogastrique-spinal). Rev. neurol., 1918, xxxiv, 117–148.
13. Weisenburg, T. H.: Cerebello-pontile tumor diagnosed for six years as tic douloureux. The symptoms of irritation of the ninth and twelfth cranial nerves. Jour. Am. Med. Assn., 1910, liv, 1600–1604.

LESIONS AFFECTING THE VAGUS NERVE

WILLIS S. LEMON

WHEN an internist attempts to interest specialists he must necessarily choose for his subject the lesions of an anatomic structure which is of common interest. For this reason I have chosen lesions affecting the vagus nerve, and shall attempt to describe those in particular which produce symptoms in the course of the nerve from the jugular foramen to the arch of the aorta.

Tilley has recently described incidences of recovery from involvement of the recurrent laryngeal nerve with paralysis, and has attempted to explain the recovery on the basis of a temporary lesion which he believes is probably due to involvement of the crico-arytenoid joint, or to peripheral neuritis of unknown origin. I have not observed this type of disease and, although I have noticed improvement particularly of pressure symptoms after the removal of tumors, I have not observed complete recovery. The vagus nerve is not often affected by primary isolated neuritis, and I have not seen cases that could be classified as similar to the primary neuritis of the seventh nerve. It is true that the general neuritis which accompanies alcoholic poisoning, or follows diphtheria, or even intoxications such as lead and arsenic, has been recognized; this has been referred to by Taylor. It is also recognized that the nerve may take part in a general neuritis resulting from tumor, aneurysm of a vertebral artery, or meningitis, but in such instances neighboring nerves, especially the ninth, eleventh, and twelfth, may be involved in the process, owing, of course, to the close association in the origin of the several nerves and to their approximation in the jugular foramen.

Conditions within the bulb itself will not be described here, but softening of the bulb, hemorrhage, multiple sclerosis, bulbar

paralysis, and tabes have been mentioned as etiologic factors in diseases of the nerve. Bulbar paralysis and tabes are of particular interest to the internist and to the laryngologist, inasmuch as they are frequently called on to treat such unfortunate patients, because of difficult respiration and deglutition which so often ends in death from starvation, in bulbar paralysis, and because of the frequency of laryngeal difficulties with tabes. Greene, in 1906, reported sixty cases of tabes in which there was laryngeal difficulty in 15 per cent, crises in 12 per cent, and paralysis of one or both of the recurrent laryngeal nerves in 10 per cent. Paralysis was always in abduction and Greene believed it to be caused by degeneration of the recurrent nerve, and that the abductor muscles were first involved because, being the weak group, they succumbed earlier. It is not exactly determined why the laryngeal symptoms show evidence of such varying phenomena, but it is probably owing to both central and peripheral causes. The syphilitic patient is subject to peculiar spasmodic or even continuous dyspnea when the upper respiratory passages of the lungs are affected, and some of them may die during the first or, more commonly, after repeated attacks.

The symptoms of damage to the vagus nerve must necessarily be varied because of the length, associations and multiple functions of the nerve, and because true paralysis is rather a rare finding. With such a condition, any one or several of the branches innervating the respiratory or circulatory organs or the viscera may be involved and the associated nerves be weak. Fundamental functions such as the respiration are usually affected only by bilateral lesions. The patient having unilateral disease may present himself with signs of unilateral weakness in the palate, the soft palate being flaccid and hanging away from the affected side, and with unilateral weakness of the larynx so that speech is nasal. Although aphonia may not obtain, yet the voice is altered weak, and easily fatigued. If the pharyngeal branches are involved in paralysis of either the vagus or the recurrent nerve there will be difficulty in swallowing. Damage to the vagus may affect the heart, producing either increase or decrease in rate, or in bilateral lesions, the respiration

itself. In the specific examples which will be given later no characteristic signs of this nature were present and neither the heart rate alone nor the blood-pressures, could be considered as a criterion of disease of the vagus nerve. Inasmuch as the sensation may be disturbed by the effect on the sensory fibers in the nerve, there may be partial anesthesia in the pharynx and larynx, and laryngismus. I have noted certain peculiar phenomena with disease which brings pressure on the root of the lung. Children with tuberculous glands have three types of cough: (1) resembling whooping-cough, but without whoop, (2) croup, continuous and paroxysmal, and (3) continuous asthma. This asthma seems similar to that described by Kopp in his discussion of the pressure effects of enlargement of the thymus, and known as Kopp's asthma. Such phenomena are common to all types of glandular disease, including tuberculosis, Hodgkin's disease, and the adenopathy of leukemia. Dyspnea and cough may become very serious. In a recent case of Hodgkin's disease dyspnea became so extreme that there were signs of actual air hunger. Examination revealed very positive evidence of enlargement of the tracheobronchial lymph-glands. In this particular instance, at the height of the paroxysm, on three occasions, material resembling glands was expectorated with relief. Histologic examination revealed lymphoid cells in the material. Such a syndrome is similar to that described by Elliot in the case of calcareous glands with erosion through the wall of the bronchus. The second peculiar influence of pressure, presumably on the vagus is the dyspnea, cyanosis and cough that not infrequently appear in cases of tumors of the lung. Recently two such cases have been seen in the Clinic. Landis described instances of this type. "At the autopsy not more than a half-dozen nodules, the size of an English walnut, were found in each lung. The primary disease consisted of a small scirrhous carcinoma in the left breast. The cause of the dyspnea and cyanosis in such cases is not understood." Since the vagus nerve provides innervation for the stomach, intestines, and upper portion of the colon, gastric symptoms occasionally develop, and there may be vomiting, loss of appetite or excessive hunger, with

epigastric pain. Such symptoms have been found infrequently in the series of cases presented.

Lesions of the superior laryngeal branch of the nerve coming from the ganglion of the trunk are not common, probably because of the short length of this nerve, but when present, are evidenced by anesthesia of the larynx and laxness of the cord on the side affected, this latter sign being due to the motor branch that supplies the cricothyroid muscle which is a tensor of the cord. When the tilting action of the cricothyroid is lost, the cord becomes flaccid, and the voice is altered in pitch and easily fatigued. Following the general rule for recovery in paralysis, sensation is first regained. In the larynx this is probably because the mucosa is innervated from both superior nerves.

INFERIOR OR RECURRENT NERVES: EMBRYOLOGIC CONSIDERATIONS

When the two inferior nerves develop in fetal life, they both take up their position at about the fourth aortic arch of the corresponding side, and therefore are placed symmetrically temporarily. During the development of the fetus the left arch becomes the arch of the aorta, while on the right it becomes the subclavian. For this reason the nerves, although retaining their original anatomic associations, alter their relation to other structures because of the lack of symmetry in growth and the downward displacement, especially on the left.[12]

ANATOMIC CONSIDERATIONS

The recurrent nerves, particularly on the left side, are subject to pressure because of the anatomic design of the mediastinum and the root of the neck. This is true because of the confined space in which so many important structures are to be found, and because in the central portion where the left recurrent nerve takes its course, there is a marked degree of fixation of the parts and a consequent lack of ability to escape pressure. Moreover, it is an area that is bounded both front and back by bony structures that do not yield easily to pressure, and the anteroposterior

diameter in this location is little more than half that of the thorax in an off-center position. Finally, it is the point at which numerous types of disease, both benign and malignant, are found, as well as those incident to circulatory damage. It is evident that the nerve on the right side should not be affected as often as on the left, because it is not in a central position and it is out of the area affected by the diseases mentioned. It is, however, peculiarly liable to damage from tuberculous disease because of its close proximity to the pleura. It will be remembered that the apex of the lung on the right side is 3 cm. closer to the trachea than on the left, where it is separated because of the lateral position of the esophagus and the interposition of the aorta, internal carotid artery, and lymphatic and areolar tissue.[10] The relationship of the two nerves in the neck are similar, inasmuch as they pass upward by the side of the trachea; on the right side from before backward around the subclavian, and upward to the trachea behind the common carotid, and either behind or, in front of, the inferior thyroid artery, and on the left, ascending the side of the trachea between it and the esophagus.

In the usual discussion of causes for laryngeal symptoms and signs, "aneurysm" and "tumor" are the general terms used to account for this condition. I wish to show more specifically the causes of a number of such signs. The histories which follow are those of patients who have been examined routinely in the Clinic. Any of these patients might have been referred primarily to an internist or a laryngologist.

CASE REPORTS AND COMMENTS

Case 1 (A285410). A. W., a man, aged thirty-five years, came to the Clinic because of hoarseness and a lump back of the right ear. He complained of deafness, noises and sharp pains in the right ear. He was dizzy, had orbital as well as frontal headaches above the right eye, was dyspneic without exertion, had a non-productive cough, difficulty in swallowing, and suffered from pain in the right shoulder. The systolic blood-pressure was 110, the diastolic 80, and the pulse-rate 80. He had an aural polypus and enlarged glands below the auricle. The right eye showed evidence of lagophthalmus. Atrophy and fibrillation of the right trapezius was observed as well as atrophy of the tongue. The blood Wassermann reaction was negative

and a roentgenogram of the chest was reported negative. Right recurrent nerve paralysis with fixation of the right cord was observed. Following operation the pathologist made a diagnosis of mixed tumor of the parotid.

Comment.—The symptoms and signs were explained by the presence of a tumor of the mixed type derived from the parotid gland. Pressure had damaged the nerve, producing right cord paralysis and the syndrome of Jackson with involvement of the eighth, ninth, tenth, eleventh, and twelfth nerves and a partial involvement of the sympathetic. Following operation involvement of the seventh was observed. Various syndromes may develop in the location of the tumor, depending on the extent of damage to the various associated nerves. The cord is found in the cadaveric or intermediate position in conditions that injure the vagus nerve between the point above where the superior laryngeal nerve is given off and the jugular foramen.

Case 2 (A252564). B. E. T., a man, aged twenty-seven years, came to the Clinic December 10, 1918, complaining of difficulty in breathing of seven weeks' duration. He appeared to be in extremis, his stridor could be heard at a distance, he had air hunger and the typical signs of inspiratory obstruction that appear in the thorax. Tracheotomy was performed at once to relieve his dangerous respiratory embarrassment. The heart was found to be enlarged; and a roentgenogram of the chest confirmed the clinical observation. The blood Wassermann reaction was positive. Bilateral abductor paralysis was present, but under treatment for syphilis the cords regained almost complete function. The tracheotomy tube was removed June 20, 1920.

Comment.—In bilateral abductor paralysis the cords lie in the middle line and act as a valve, actually closing the larynx when inspiration is attempted. Aphonia, stridor, and extreme respiratory difficulty are characteristic of this form of paralysis if central or peripheral in origin and the result of injury to both recurrent nerves. It is an illustration of one of the effects of syphilis on the vagus.

Case 3 (A369480). M. H., a woman, aged twenty-five years, came to the Clinic on several occasions, the first time on June 19, 1922. She complained of a tumor that had developed on the left side of the neck. A diagnosis of tuberculosis had been made elsewhere and the gland was thought to be tuberculous. Repeated observations confirmed the diagnosis of glandular tuberculosis, but no evidence of the disease was found in the lungs. Because of continuous ill health removal of the gland was advised. At operation the tumor was found to lie in the region of the carotid body and considerable difficulty was experienced in dissecting it away, especially from the vagus and the sympathetic trunks. The pathologist reported a degenerating neurofibroma. February 7, 1923 the patient made a second vist; she complained of weakness, fatigue, cramps in the stomach, and nausea. She found it difficult to swallow fluids without choking, and if care was not exercised she strangled at meals. Coughing was productive of a small amount of sputum. The systolic blood-pressure was 120, the diastolic 82, and the pulse 92. The left pupil was smaller than the right, although there was no relative difference in response to cocain dilatation. The palpebral fissure was narrowed on the left so that both eyelids approached the corneal circum-

ference. The reaction to light and to accommodation was retained. The sensation of the larynx was normal, but the left cord was found in the cadaveric position and thought to be the result of pneumogastric nerve injury.

Comment.—These observations illustrate the effect of damage to the nerve as it proceeds downward in the carotid sheath. As a result of injury pharyngeal, laryngeal, and circulatory symptoms developed, the most distressing of which was the difficulty in swallowing without strangulation. The lesion of the sympathetic was evidenced by the signs appearing in the left eye.

Case 4 (A340269). H. B., a man, aged twenty-eight years, came to the Clinic November 9, 1920, complaining of a lump in the neck that had been growing rapidly for the previous four months. At examination several discrete, enlarged, hard glands were found on the left side of the neck, largest and hardest in the region of the left lobe of the thyroid (5 by 7 by 2 cm.). The glands on the right side of the neck were small, the right axillary glands were enlarged, and a tumor was present in the suprasternal notch. The patient was hoarse, and the left cord of the larynx fixed from a total paralysis of the recurrent nerve. The diagnosis was "thyroid enlargement; malignancy may be primary with glandular metastases."

Case 5 (A317945). Mrs. J. M., aged fifty-seven years, came for examination June 1, 1920, complaining of choking spells that came suddenly every three or four days, accompanied by congestion and blueness of the face lasting for from five to ten minutes. She believed that swallowing precipitated the attacks. She was hoarse and complained of cough. The systolic blood-pressure was 156, the diastolic 100, and the pulse-rate 78. She had a moderately enlarged goiter, especially in the region of the isthmus and the right lobe. Roentgenograms of the chest proved the absence of substernal involvement, and the presence of cardiac enlargement, the shadow measuring 15 cm. on the plate. The Wassermann reaction was negative. Examination of the larynx revealed a fixed right cord from right recurrent nerve damage. "Adenoma of right lobe of thyroid. Right recurrent nerve paralysis," was the diagnosis. The pathologist described the tissue removed at operation as multiple, hemorrhagic, degenerating, cystic, fibrous, fetal and colloid adenomas.

Case 6 (A346051). M. W., a man, aged sixty years, was examined January 12, 1921, because of shortness of breath, cough and enlargement of the neck. It was found that he was not only dyspneic, but orthopneic; his cough was harassing and productive of blood-flecked sputum. There was a tumor low in the right side of the neck, the larynx was displaced to the right and the mediastinal area of dulness was increased, especially to the right of the middle line. On coughing, a tumor was displaced upward and rose above the clavicle. The systolic blood-pressure on the right side was 170, the diastolic 90, and the pulse-rate 48; on the left side the systolic was 190, the diastolic 90, and the pulse-rate 50. The Wassermann reaction was negative and roentgenograms of the chest revealed the presence of a nonpulsile tumor of the mediastinum. The right cord was fixed, and movement of the right arytenoid limited. The left cord was limited in movement and failed to abduct completely, and the larynx as a whole was displaced

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laterally to the right. A diagnosis was made of large substernal goiter containing multiple adenomas.

Case 7 (A394065). Mrs. L. G., aged forty-five years, came for examination June 30, 1922, complaining of a tumor in the neck, attacks of indigestion, recent acute facial neuralgia, hoarseness, weakness, blurred vision, diplopia, and dysphagia. The systolic blood-pressure was 120, and the diastolic 80. A firm, fixed tumor was found in the region of the left lobe of the thyroid. There were hyperemia and blurring of the optic disks and slight swelling (about 1 diopter) particularly of the upper portions. The examiner thought an early choked disk was present. Roentgenograms of the chest revealed the presence of multiple metastasis, and the examination of the larynx revealed fixation of the left cord in the position of abductor paralysis and a lateral deviation of the larynx to the right. A diagnosis was made of carcinoma of the thyroid with metastasis to the lungs and brain.

Comment.—Cases 4 to 7 inclusive illustrate the effect of pressure from tumors of any character on the nerve as it is found within the neck below the ganglion of the root. Tumors of the thyroid gland are, of course, particularly likely to cause such a paralysis, inasmuch as they are closely associated with the thyroid cartilage, the cricoid, and the trachea. There is, therefore, great danger in removing such glands or tumors, and even in ligating, especially of the right inferior thyroid artery, because the right recurrent nerve passes either in front of, or behind, this vessel in the site usually chosen for operation. Damage of the nerve in this group produced not only laryngeal, but respiratory, circulatory, and gastro-intestinal symptoms and involvement of the recurrent nerve, whether right or left, depended on the site of the tumor. The blood-pressure and pulse-rate seem to be very little if at all disturbed. These cases serve to illustrate the fact that tumors in the lung tend to metastasize to the brain and that the thyroid gland, when in the substernal position, is often a movable body. It is the only mediastinal tumor that moves with deglutition. The vocal cord is usually in the middle line position if the nerve has been completely paralyzed as a result of chest conditions. This may be proved in postoperative goiter cases. In a few cases the vocal cord may for a time take the cadaveric or intermediate position, but within three to four months it is found in the middle line.

Case 8 (A317856). N. Z., a boy, aged fourteen years, came to the Clinic June 4, 1920 complaining of hoarseness, palpitation of the heart, and shortness of breath. The history and the examination revealed progressive hoarseness, loss of weight, palpitation, and dyspnea. The patient was subject to night-sweats and had had a cough, particularly annoying in the morning. The systolic blood-pressure was 114, the diastolic 62, and the pulse-rate 92. The heart was enlarged, measuring 9 cm. across at the level of the second rib; maximal measurements were 4.5 cm. to the right and 11 cm. to the left of the middle line. A thrill was felt and a loud reverberating murmur heard at the apex. Decreased resonance was found at both apices and râles were heard over the apex of the left lung. The Wassermann reaction was negative. A roentgenogram of the chest revealed signs significant of tuberculosis in the upper lobe of the left lung, and the enlargement of the heart. The left pupil was enlarged and the left vocal cord paralyzed. A diagnosis was made of chronic mitral endocarditis with stenosis.

Case 9 (A315233). Mrs. H. R. J., aged thirty-four years, came for examination May 10, 1920, complaining of shortness of breath, hoarseness, cough, productive of blood-streaked sputum, dizziness, pain over the precordium, palpitation, and vomiting. The systolic blood-pressure was 110, the diastolic 60, and the pulse-rate 90. A marked heaving impulse was seen over the precordium and a systolic murmur heard that was transmitted to the left axilla. The heart was enlarged, moist râles were heard throughout both lungs, and the lower extremities were edematous. The Wassermann reaction was negative and a roentgenogram of the chest revealed enlargement of the heart to the left. The left vocal cord was fixed in position of recurrent nerve paralysis. A diagnosis was made of chronic mitral endocarditis with stenosis.

Comment.—Cases 8 and 9 illustrate the fact that damage may occur to the recurrent nerves from one type of heart lesion, mitral stenosis. This fact was first shown by Ortner in 1897, and in the following year by Herrick, who reported two cases, in one of which chronic adhesive pericarditis was found, besides dilatation of the left auricle. Originally observers believed that the damage was due to pressure on the nerve by the distended left auricle impinging against the arch of the aorta. Fetterolf and Norris, however, proved quite conclusively that such pressure would be a very difficult, if not an impossible explanation and any one studying the anatomy of the parts must agree with their argument. They concluded: "The indirect mechanism may be variable, but when compression is accountable for the recurrent paralysis it must always be caused by the nerve being squeezed between the left pulmonary artery and the aorta or the aortic ligament. Anything which will dilate or force upward the left auricle, the left upper pulmonary vein, or the left pulmonary artery would tend to cause the condition," and finally, "the anatomic relationships are such that direct pressure of any portion of a dilated left auricle upon the aortic arch is impossible." Cases of bilateral paralysis of the recurrent nerves have been described. I have not seen such a case and would find it difficult to explain the condition.

Case 10 (A383057). J. C., a man, aged fifty-two years, came to the Clinic complaining of difficulty in breathing through the nose, change in the character of his voice, and a severe cough of several years' duration. The systolic blood-pressure was 130, the diastolic 70, and the pulse-rate 56. The chest was the typical barrel-shaped type with poor bilateral expansion and of such hyperresonant quality on percussion that the heart area could not be determined with accuracy. Roentgenograms of the chest gave evidence of pleural adhesions to the pericardium on the left side at the fourth interspace, and showed that the heart itself was displaced to the right. There was complete recurrent nerve paralysis on the left with the vocal cord in the middle position. A diagnosis was made of emphysema and adhesive pericarditis.

Case 11 (A323323). F. McE., a man, aged forty-five years, came to the Clinic July 6, 1920, complaining of hoarseness. The systolic blood-pressure was 145, the diastolic 50, and the pulse-rate 84. The arteries were markedly thickened, a capillary pulse was noticed, and pistol shot sound was heard over the femoral arteries. The heart was enlarged with the apex in the

seventh interspace. There was a thrill over the precordium and a systolic and disatolic murmur. Retraction of the precordium was seen at the apex, as well as retraction posteriorly, sufficiently conclusive to diagnose positive Broadbent sign. Roentgenograms of the chest revealed a dilated aortic arch and innominate artery. Because of these findings investigation was instituted to determine whether or not syphilis could be considered an etiologic factor, but it was essentially negative. The vocal cord was in the position resulting from a left recurrent paralysis. Diagnosis was made of aortic endocarditis, adhesive pericarditis, with dilatation of the aortic arch and innominate artery.

Comment.—In the first case of mitral stenosis described by Herrick that produced recurrent paralysis, pericarditis was llkewise present. In our first case (Case 10), such a condition obtained in association with emphysema, which made the examination of the heart very difficult because of inability to percuss its outlines, and the diagnosis was made by means of the roentgen ray. In Case 11 the condition was associated with aortic endocarditis and dilatation of the innominate, the entire mechanism resulting from adhesive pericarditis, or from the effect of the dilatation of the arch, which might produce stretching of the left recurrent nerve with resultant vocal cord paralysis.

Case 12 (A305042). Mrs. E. R. R., aged forty-eight years, was examined February 2, 1920. She complained of hoarseness, dizziness, and choking on deglutition. The heart sounds were transmitted over the right upper chest. There was a systolic bruit at the supraclavicular area and broadened mediastinal dulness. No thrill or expansile pulsation could be felt on palpation. The fingers of the right hand were clubbed, but those on the left hand were normal, and the veins on both sides of the neck were dilated. The systolic blood-pressure on the right side was 164, the diastolic 112, while on the left side the systolic was 172, the diastolic 104, and the pulse-rate 100. A roentgenogram of the chest revealed a tumor in the upper right mediastinum with dilatation of the aorta and probable aneurysm of the innominate artery. The right vocal cord was fixed from right recurrent nerve damage, and the right arytenoid was slightly swollen. The left cord was normal in appearance and movements.

Comment.—I have observed but one case of this type, the result being due to an innominate aneurysm with resulting paralysis of the right laryngeal nerve. Associated with this paralysis were laryngeal, esophageal, and cardiac symptoms and signs. This also is the only instance of unilateral clubbing of the fingers that I have observed.

Case 13 (A303571). J. M. S., a man, aged forty-six years, came to the Clinic January 23, 1920, complaining of hoarseness and shortness of breath. The systolic blood-pressure on the right was 146, the diastolic 58; on the left the systolic was 134, the diastolic 44, and the pulse-rate 76. Examination revealed throbbing carotids, heaving pulsation over the upper precordium, enlarged veins over the sternum, brassy cough with tracheal tug, murmurs at all the valve areas and a capillary pulse with pistol shot phenomena over the femorals. The heart at the level of the second rib measured 6 cm. to the right of the middle line, 4 cm. to the left, and at the level of

the sixth rib, 7 cm. to the right and 14 cm. to the left of the middle line. A roentgenogram of the chest revealed an aneurysm of the arch of the descending aorta. Paralysis of the left vocal cord was seen, being completely fixed. The Wassermann reaction was negative.

Comment.—A large number of cases of aneurysm has been seen in which evidence of recurrent paralysis was noticed. One case is reported from this group. Aneurysms in the transverse portion of the arch are of course peculiarly liable to produce symptoms because of the close anatomic relationship between the nerve and the arch. It will be remembered that the nerve is closely associated with the arch and passes from before backward, just anterior to the ligament.

Case 14 (A318728). H. O., a man, aged sixty years, came to the Clinic June 7, 1920, complaining of dyspnea, cough, and weakness. Stridor could be heard, and on percussion increased mediastinal dulness was demonstrated. Dulness was also found at the right base. Examination of a supraclavicular gland revealed it to be inflammatory, but tissue from the mediastinum was reported by the pathologist to be carcinomatous, having the appearance of epithelioma. The systolic blood-pressure was 140, the diastolic 80, the pulse-rate 84; the temperature varied from 99° to 103° F. Roentgenograms revealed thickened pleura at the right base; there was an apparent collapse of the right lung as well as a mediastinal tumor. The vocal cords were edematous, and the left cord was apparently paralyzed or ankylosed. The clinical diagnosis was inflammatory thickening of the pleura and mediastinum, and the operative diagnosis was carcinoma of the mediastinum.

Comment.—Malignancies of the mediastinum are not materially different in type or age of incidence from malignancies elsewhere, though primary carcinoma is extremely rare. In Case 14 the tumor was found to be a carcinoma on tissue examination.

Case 15 (A245608). T. C. P., a man, aged twenty-three years, came to the Clinic September 13, 1918, complaining of shortness of breath, epigastric pain, flushing of the face on stooping, and a brassy cough. The systolic blood-pressure was 125, the diastolic 80, the pulse-rate 130, and the temperature 100° F. Large glandular enlargements were found in the right supraclavicular area, left cervical, right axillary, and both inguinal regions. The liver was enlarged and there was bilateral mediastinal dulness. The Wassermann reaction was negative. Roentgenograms confirmed the physical findings by revealing a bilateral mediastinal tumor that extended to the middle clavicular line on both sides, and reached nearly to the base. A diagnosis was made of Hodgkin's disease, with laryngeal pressure.

Comment.—Many cases of Hodgkin's disease have been observed in the Clinic. In 1921 Doyle and I reported twenty-six cases that affected the mediastinum. Laryngeal changes, however, are somewhat rare with the exception of those symptoms described, which are probably due to the effect of pressure on the trachea and bronchi. The peculiar attacks of dyspnea that sometimes appear have been discussed. It would seem that Hodgkin's disease does not produce the pressure effects of other tumors, probably because of the tendency to gland isolation rather than amalgamation, and the absence of solidarity and infiltration.

Case 16 (A355483). R. G. V., a man, aged fifty-six years, came to the Clinic complaining of hoarseness of one year's duration, weak voice, dyspnea on exertion, and loss of weight and strength. The systolic blood-pressure was 154, the diastolic 110, and the pulse-rate 78. Moist bubbling râles were heard throughout the right lung and the base of the left lung, and lack of chest expansion was noted. Enlarged cervical nodes were felt, especially a gland above the inner third of the right clavicle. A roentgenogram of the chest showed a diffuse coarse infiltration of the whole right side, rather less marked on the left side, which was indicative of miliary carcinomatosis. The left cord was fixed in a position of complete abductor paralysis from complete paralysis of the recurrent nerve. An ulcer on the right arytenoid was believed to be metastatic. A diagnosis was made of mediastinal carcinoma either from the thyroid or thymus, with metastasis to the lungs and larynx. The possibility of the carcinoma being primary in the lung was considered.

Comment.—This group of tumors of the lung has been discussed and Case 16 is an illustration of the type that occasionally is seen, namely, miliary carcinomatosis. Complete abductor paralysis of the left cord was observed, as well as an ulcer on the right arytenoid, which was probably metastatic in character.

Case 17 (A356536). M. E. R., a woman, aged fifty-three years, came to the Clinic April 27, 1921, complaining of a tumor in the outer quadrant of the right breast. Operation was performed April 30th, and a malignant tumor, which involved the axillary gland, was removed. The patient returned to the Clinic March 16, 1923, with a chronic nonproductive brassy cough, hoarseness, and dyspnea. Her voice was husky. The systolic blood-pressure was 162 and the diastolic 112. The right arm was swollen; there were enlarged glands in the supraclavicular region, and an increased mediastinal dulness on both right and left sides. A roentgenogram of the chest revealed coarse infiltration of the first and second interspaces on the right side, and marked increased density at the right base to the level of the third rib anteriorly. No paralysis was found on examination of the larynx. A diagnosis was made of extensive mediastinal metastasis, and recurring carcinoma of the right breast. The cause of the dyspnea was attributed to infiltration or irritation of the laryngeal nerve.

Comment.—Case 17 illustrates the tendency of carcinoma of the breast to cause metastasis in the chest with pressure irritation or infiltration of the laryngeal nerves. Any person having carcinoma of the breast and complaining of dyspnea and chronic cough, nonproductive in its early course, should be suspected of having developed mediastinal metastasis.

Case 18 (A336135). T. J., a man, aged twenty-six years, came for examination because of hoarseness of two months' duration. He had been operated on because of tuberculous disease at the costosternal juncture with the fourth costal cartilage, and unclosed sinuses remained. The systolic blood-pressure was 120, the diastolic 76, and the pulse-rate 108. A tumor presented on the anterior wall of the chest with what appeared to be tuberculous sinuses over the sternum and ribs on the right side, and there was evidence of mediastinal supraclavicular and axillary adenopathy. The Wassermann reaction was negative. A roentgenogram of the chest revealed

thickening at the hilus, and there was a complete recurrent paralysis on the left side. A diagnosis was made of tuberculous tracheobronchial, cervical and axillary glands, tuberculous sinuses on the anterior right side of the chest, and recurrent nerve paralysis on the left.

Case 19 (A377493). S. K., a man, aged forty-two years, came to the Clinic November 16, 1921, complaining of cough, sore throat, hoarseness, dyspnea, and hemorrhages. The systolic blood-pressure was 100, diastolic 56, and the pulse-rate 100. Both lungs were infiltrated with a cavity at the right apex; the bacillus of tuberculosis was present in the sputum. A roentgenogram of the chest confirmed the findings of extensive tuberculosis of both lungs with cavities in both upper lobes, and the examination of the larynx revealed complete recurrent paralysis on the left side with thickening of the right cord, suggesting possible ulceration. A diagnosis was made of extensive bilateral pulmonary tuberculosis with cavity formation. Fibrosis was the probable cause of the paralysis.

Comment.—Of the cases of tuberculosis chosen for discussion, Case 18 is a wide-spread glandular type, and Case 19 a chronic ulcerative disease of the lung. On the left side tuberculous glands are particularly likely to affect the nerve because a gland is normally found between the bronchus anteriorly and the recurrent nerve posteriorly (Fetterolf and Norris). On the right side, proximity of a tuberculous apical pleura to the nerve is responsible for the frequency of right vocal cord paralysis.

Case 20 (A405187). O. R., a man, aged twenty-five years, came to the Clinic complaining of pain in the left arm, dry cough, and husky voice. His systolic blood-pressure was 116, the diastolic 90, and the pulse-rate 100. He had pain in the left shoulder which was referred down the arm to the fingers, and pain and tenderness around the left chest, following the third, fourth, and fifth intercostal nerves and passing from the back to the sternum. The orbital fissure was narrowed, the upper lid was ptosed, and the right pupil was twice the size of the left, although both pupils reacted to light and accommodation. No perspiration or flushing appeared on the left side of the face or left arm after exercise, although there was normal moisture on the right side. There was diffuse enlargement of the thyroid and evidence of tumor in the left upper chest with venous engorgement over the left chest. The Wassermann reaction was negative. A roentgenogram of the chest revealed a large solid tumor in the upper part of the left mediastinum, extending to the periphery of the chest. The left vocal cord was paralyzed. A diagnosis was made of sarcoma. Substernal thyroid and encapsulated empyema were considered. Aspiration of the tumor showed no evidence of fluid. Sympathetic nerve root and recurrent laryngeal nerve paralysis were associated.

Case 21 (A405006). Mrs. N. S., aged thirty-eight years, came to the Clinic because of pain over the left chest, hoarseness, cough, nausea, vomiting, and sleeplessness. The systolic blood-pressure on the right was 108, the diastolic 70; on the left, the systolic was 110, the diastolic 72, and the pulse-rate 98. The condition had been diagnosed bronchitis. The cough was at first nonproductive in character, but it was continuous, and the sputum was mucopurulent, then blood-streaked. Clubbed fingers and exophthalmos were noted and the left pupil was larger than the right. Restricted respira-

tory movements were seen over the left chest and the veins on this side of the chest were enlarged. There was clinical evidence of a large tumor in the left upper chest. The spleen was palpable. The Wassermann reaction was positive. Roentgenograms of the chest showed evidence of a tumor involving the whole upper left lobe, and probable metastasis in the region of the right diaphragm. The left cord was in the middle line position. A diagnosis was made of malignancy of the left chest with metastasis on the right, left recurrent nerve paralysis, and syphilis. The possibility of visceral gumma of the lung was entertained.

Comment.—Sarcoma likewise affects the mediastinum, and lymphosarcoma is probably the most common tumor found in this region. In one of the two cases (Case 20) chosen as represenative of this series there was nerve root as well as recurrent laryngeal involvement. The damage to the sympathetic nerve was evidenced by the condition of the pupils and of the moisture of the skin. It would seem that in this case paralysis of the sympathetic fibers had obtained, inasmuch as the pupil was retracted rather than dilated, and no perspiration appeared on that side of the face. This observation is the reverse of the usual findings as reported by New and Bozer in their work on hyperhidrosis of the face. Aspiration was done in Case 20 because of the well-known fact that an empyema may become encapsulated and simulate mediastinal tumor. Case 21 was complicated by the fact that the patient had a positive Wassermann reaction although the tumor itself seemed undoubtedly malignant.

Case 22 (A336603). C. O. C., a man, aged fifty years, complained of difficulty in swallowing, loss of weight, and weakness. The systolic blood-pressure was 118, the diastolic 80, and the pulse-rate 84. An obstruction 19.38 cm. from the incisor teeth was found on examination of the esophagus. The Wassermann reaction and roentgenograms of the chest were negative. The left cord was fixed, and marked edema of the posterior part of both arytenoids was noted. A diagnosis was made of carcinoma in the upper part of the esophagus.

Case 23 (A380246). Mrs. F. L., aged thirty-seven years, came for examination because of inability to swallow, shortness of breath, and croupy cough. Glands from the right cervical region had been removed four years before. She vomited after eating and had a feeling of a defect in the esophagus at the level of the angle of Louis, which caused strangulation and regurgitation. Food had been retained in the "sac" for from twenty-four to thirty-six hours. A gurgling sensation indicated the passage of food beyond the sac. The systolic blood-pressure was 112, the diastolic 82, and the pulse-rate 76. Examination revealed glands in the right supraclavicular region, enlarged mediastinal dulness and a palpable spleen, and roentgenograms of the chest revealed healed tuberculosis of both lobes and thickened pleura at the right base. The esophagus was obstructed 14.5 cm. from the incisor teeth. A thread was coughed from the trachea, indicating the presence of an esophagotracheal fistula. The right vocal cord was in bilateral abductor position. The pathologic report on the gland that was removed for diagnosis was lymphosarcoma. A diagnosis was made of lymphosarcoma with involvement of neighboring glands, and esophagotracheal fistula.

Comment.—The two cases of malignancy of the esophagus illustrate the fact that fistula and obstruction may develop, and that the cords may become involved in the infiltrative process.

The foregoing representative cases were chosen from fifteen groups because they seemed to represent typical changes in the nerve, and to illustrate the symptoms that may be expected at various points in its course. They also illustrate the various types of disease that may be of common interest to the internist and the specialist.

BIBLIOGRAPHY

1. Elliott, A. R.: Broncholithiasis. Jour. Am. Med. Assn., 1922, lxxix, 1311–1314.
2. Fetterolf, G., and Norris, G. W.: The anatomical explanation of the paralysis of the left recurrent laryngeal nerve found in certain cases of mitral stenosis. Am. Jour. Med. Sc., 1911, cxli, 525–638.
3. Greene, D. C., Jr.: A study of the larynx in tabes. Boston Med. and Surg. Jour., 1906, cliv, 97–99.
4. Herrick, J. B.: Report of a case of concretio cordis and mitral stenosis, with recurrent laryngeal paralysis from pressure of fibrous bands and an enlarged left auricle. Chicago Med. Recorder, 1898, xiv, 192–196.
5. Kopp: Quoted by Norris and Landis, p. 559.
6. Landis, H. R. M.: In: Norris, G. W., and Landis, H. R. M.: Diseases of the chest. 2 ed. Philadelphia, Saunders, 1920, p. 562.
7. Lemon, W. S., and Doyle, J. B.: Clinical observations of Hodgkin's disease with special reference to mediastinal involvement. Am. Jour. Med. Sc., 1921, clxii, 516–525.
8. New, G. B.: The larynx in diseases of the thyroid. Ann. Clin. Med., 1923, i, 262–265.
9. New, G. B., and Bozer, H. E.: Hyperhidrosis of the cheek associated with injury to the parotid region. Minnesota Med., 1922, v, 652–657.
10. Norris, G. W.: In: Norris, G. W., and Landis, H. R. M.: Diseases of the chest. 2 ed. Philadelphia, Saunders, 1920, p. 49.
11. Ortner, N.: Recurrenslähmung bei Mitralstenose. Wien. klin. Wchnschr., 1897, x, 753–755.
12. Piersol, G. A.: Human anatomy. 5th ed. Philadelphia, Lippincott, 1916, 2104 pp.
13. Taylor, E. W.: Pneumogastric (vagus, tenth) nerve. Osler's Modern Medicine. Philadelphia, Lea & Febiger, 1910, vii, 571–579.
14. Tilley, H.: Some observations on the clinical significance of paralysis of the left vocal cord. Jour. Laryngol., 1918, xxxiii, 161–166.

INVOLVEMENT OF THE NERVOUS SYSTEM IN MALIGNANT DISEASE OF THE NASOPHARYNX*

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THE frequency with which malignant disease of the nasopharynx occurs and its extremely varied and misleading symptoms do not seem to be generally appreciated. New has recently directed attention to the relation of this condition to general diagnosis; such relation applies particularly to neurologic diagnosis. Of prime importance is the fact that often there are no symptoms referable to the nasopharynx that would serve to assist in making a correct diagnosis. From the neurologic standpoint, these cases may be classified in four fairly well-defined groups.

Group 1.—This type is spoken of in the literature as "the neuralgic type." Pain is perhaps the most common symptom and may be referred to the ear, the side of the head, or the face.

Group 2.—Ocular manifestations, such as diplopia, ptosis, exophthalmos, and blindness, are characteristic of this group. Such symptoms may be transitory, and for many months the monosymptomatic expression of a malignant growth in the nasopharynx. Case 1 (A371779) is an example of this type (Fig. 63). A man, aged thirty-five years, came to the Clinic September 20, 1921 because of headache and diplopia owing to palsy of the left external rectus of two months' standing. He had no nasopharyngeal symptoms. In the vault of the nasopharynx was a highly malignant, squamous-cell epithelioma.

Group 3.—The cases in this group are of the glossopharyngolaryngeal type. The patients complain of dysarthria, dys-

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phagia, and recurrent aphonia due to palsies of the cranial nerves.

Group 4.—The cases in this group are miscellaneous, including epilepsy, mental disorders, and metastasis to distant parts of the nervous system. This type is represented by Case A379120 (Fig. 64). A man aged forty-six years was brought to the Clinic by his relatives December 9, 1921 because of a mental disturbance. He was normally good-natured and jovial, with con-

Fig. 63 (A371779).—Paralysis of the left external rectus muscle. No nasopharyngeal symptoms were present, although the patient had a highly malignant squamous-cell epithelioma.

siderable business acumen. Two and one-half years before he became irritable and vindictive, flew into a rage, was inveigled into a wild-cat scheme and swindled out of a thousand dollars, thought his wife was feeding him fire and tried to kill her, became morose and suicidal, lost all personal pride, and spit and defecated anywhere. During the two and one-half years he was treated with antispecific remedies as a case of dementia paralytica.

Examination revealed squamous-cell epithelioma (biopsy) of the left nasopharynx. The left cervical glands were enlarged. The patient was stupid, uncoöperative, and hoarse. Vision in the left eye was poor. The pupils did not react to either direct or crossed light, and were very small. The fundi were normal. Tactile sensibility was definitely impaired throughout the left half of the face, and there was impairment of pain

Fig. 64 (A379120).—Patient with squamous-cell epithelioma of the left nasopharynx, treated for two and one-half years for paresis.

sensibility over the second and third divisions. The right motor fifth nerve was paralyzed. A watch tick apparently was not heard on either side. Dysphagia was present, the left vocal cord was fixed. Anesthesia of the pharynx and hypopharynx was present on the left. There was incoördination in the finger-to-nose test on the left. The gait was ataxic. The Babinski and Chaddock reflexes were questionable on the left.

DIAGNOSIS

That the early diagnosis of such cases is not always easy is illustrated in Table 1, which shows that such patients are often subjected to needless operations, presumably because of a

Table 1

Erroneous diagnosis and treatment in thirty-four cases of malignant tumors of the nasopharynx with involvement of the nervous system

Diagnosis or type of treatment	Cases
Tonsillectomy	7
Extraction of teeth	7
Dissection of glands from the neck	8
Operations on the nose	15**
Trifacial neuralgia*	3
Paracentesis of the tympanic membrane	2**
"Abscess" lanced in the throat	1**
Hodgkin's disease	1
Mumps	1
Pituitary tumor	1
Dementia paralytica	1
Syphilis	1
Nasopharyngeal sarcoma	2

*Alcohol injections and nerve sections
** Several operations

mistaken interpretation of the case. A correct diagnosis had been made in but two of the cases observed at the Clinic. Trifacial neuralgia was diagnosed and treated by alcohol injections in three cases. Pituitary tumor, paresis, and syphilis of the nervous system were each diagnosed once.

The important neurologic findings are shown in Table 2. They have been discussed in detail in a previous paper.

The involvement of various nerves noted in thirty-four cases are given in order of frequency of occurrence: (1) the sixth nerve, (2) the sixth nerve and others entering the orbital cavity, (3) the nerves entering the orbital cavity, and the trigeminal nerve, and (4) the fifth nerve alone, or in combination with the jugular foramen group. All combinations of palsies of the cranial nerves seem possible. Pathologic evidence shows that involvement of these nerves is usually extracranial. Just how the dissociation in sensibility, sometimes noted, comes about in these peripheral nerve lesions remains unexplained.

Table 2

Involvement of the cranial nerves in thirty-four cases of malignant tumors of the nasopharynx

Type of tumor	Cases	Nerves involved													
		First*	Second**	Third	Fourth	Fifth (sensory)	Fifth (motor)	Sixth	Seventh	Eighth***	Vago-accessory: Palate****	Vago-accessory: Vocal cords	Eleventh (spinal)	Twelfth*****
Squamous cell epithelioma	18		3	3	3	8	4	12	1		5	1	1	4
Adenocarcinoma	1		1			1								
Lymphosarcoma	12		5	3		5	2	9	1		3	2	2	2
Sarcoma	2		1	1	1	1	1	1						
Mixed cell sarcoma	1		1	1	1			1						
Total	34	?	11	8	5	15	7	23	2	?	8	3	3	6

*The frequent nasal obstruction makes it impossible to determine involvement.

**Choked discs, bilateral twice and unilateral six times. Secondary optic atrophy, homolateral twice. Simple optic atrophy with homolateral blindness and heterolateral temporal hemianopsia once. Central scotoma three times.

***Loss of hearing and tinnitus in at least one-half of the cases, probably due to eustachian tube obstruction

****Difficult to determine because of mechanical displacement or direct involvement of the muscle by the tumor

*****In one case hemiatrophy of the tongue was the first and only complaint

Males 28; females 6. Age of patients with sarcoma, six years to sixty-three years; average age forty-nine and three-tenths. Age of patients with epithelioma thirty-five to sixty-four years, average forty-nine and one-tenth years. Onset of first symptoms in cases of carcinoma six weeks; of sarcoma four weeks; longest duration in cases of carcinoma, five years, of sarcoma, three years. Average duration one and four-tenths years, and one and two-tenths years, respectively.

The sensory disturbances noted in the domain of the trigeminal nerve are interesting (Figs. 65 and 66).

CONCLUSIONS

1. Malignant tumors of the nasopharynx are more common than is generally believed.

2. The early symptoms are often entirely extranasopharyngeal and in fully one-third of the cases lie in the field of the neurologist.

3. In all cases of unexplained cranial nerve palsies, or in paralysis of groups of cranial nerves constituting well-known

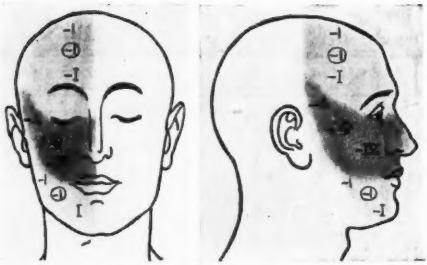

Fig. 65 (A350568).—Besides the sensory disturbances the patient had anosmia on the right; blindness, blurred disc, proptosis 4 mm., complete external and moderate internal ophthalmophagia on the right; paralysis of the right motor and fifth nerves; deafness in the right middle ear; paralysis of the right half of the palate, and slight hemiparesis of the tongue on the right.

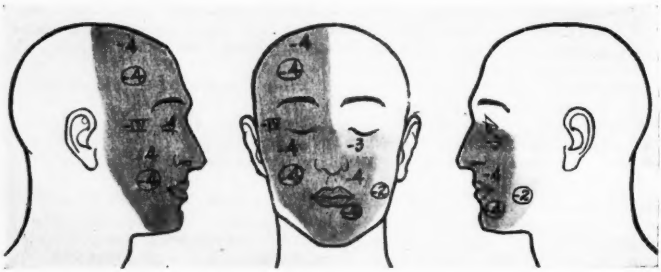

Fig. 66 (A337621).—Besides the sensory disturbance, the patient had complete external and internal ophthalmoplegia, paralysis of the motor fifth nerve, and hemiparesis, hemiatrophy, and fibrillary tremors of the tongue, on the right side.

syndromes, such as that of Jackson of Avellis, of the jugular foramen, of the retroparotid space, and in cases of metastasis to distant parts of the body, the nasopharynx should be carefully examined by an expert.

4. Pituitary tumor may be simulated, and all patients under examination for pituitary tumor should have an examination of the nasopharynx.

5. The resemblance of these cases to those due to primary involvement of the gasserian ganglion is often very close.

6. This group of cases illustrates very strikingly the value of close coöperation between the rhinologist and the neurologist. Without the coöperation of the Sections of Laryngology, Oral and Plastic, and Otolaryngology and Rhinology, the Section on Neurology would have failed utterly in the diagnosis of such cases referred primarily to it. On the other hand, a study of many of these patients cannot be considered complete without investigation by the neurologist; this is evidenced by the numerous ill-advised operations to which many of these patients had been subjected.

BIBLIOGRAPHY

1. New, G. B.: Relation of nasopharyngeal malignancy to other diagnosis Minn. Med., 1921, iv, 419–422.
2. Shelden, W. D.: Tumors involving the Gasserian ganglion. Jour. Am. Med. Assn., 1921, lxxvii, 700–705.
3. Woltman, H. W.: Malignant tumors of the nasopharynx with involvement of the nervous system. Arch. Neurol. and Psychiat., 1922, viii, 412–429.